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STUDIES ON THYROID MEDICATION I. SOME CONDITIONS DETERMINING THE HAEMATOPOIETIC EFFECTS*

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The relation of the thyroid gland to the activities of the hematopoietic tissues has for years been a subject of clinical and experimental study. The literature on the topic was reviewed up to 1929 by Hoskins and Sleeper (1) who added a report of studies on 15 patients. The literature was found consistently to indicate that in experimental animals *thyroidectomy* results in decrease in the red cell count. As regards the white cells reports both of increase and of decrease in the polymorphonuclear as well as the lymphocytic elements have been made. The literature on the whole indicates that *hypothyroidism* in man is frequently but by no means always marked by secondary anemia, leucopenia and relative or absolute lymphocytosis. Eosinophilia is occasionally but by no means characteristically found. The evidence regarding the effects of *thyroid feeding* is likewise not concordant. Most observers have reported an increase in the red cells but instances of decrease are not lacking. Deviations in both directions have been recorded for the leucocytes as well as the lymphocytes. The suggestion has been offered that the depressions in cell counts resulting from thyroid administration might be ascribed to a toxic or a fatigue effect of overly large doses. The testimony as to the hematological picture in *clinical "hyperthyroidism"* is likewise discordant. Most observers have recorded lymphocytosis. Leucopenia is a frequent but not constant finding. The reports regarding the erythrocytes are entirely conflicting. Perhaps the lack of concord on this topic is due especially to the lack of definition of the term "hyperthyroidism." Certainly the term in the clinical sense can not be equated with simple thyroid feeding.

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†With the cooperation of the Research Staff of the Worcester State Hopital.

The more recent literature is scarcely less discordant than the older. Kunde, Greene and Burns (2) have reported an extensive series of studies in rabbits. Their data convincingly indicate that high grade experimental thyroid deficiency in this species results in well marked anemia characterized by increase in the diameter of the red cells and a high color index. The possibility that the anemia was apparent rather than real, due to mere dilution, was excluded by blood volume studies. Schermann (3) also studied the effects of thyroidectomy in seven rabbits as well as two cats. He also noted a decrease in the red cell count as well as in the hemoglobin. The leucocytes at first increased sharply but in one to one and a half months returned to normal—a finding suggestive of infection. Among the white cells the proportion of "pseudo-eosinophiles" increased and of lymphocytes diminished. A fairly well marked increase in reticulocytes followed the operation but the number partially returned to normal in the course of one and a half to two months. In clinical thyroidectomy Jackson (4) noted as the sole consistency in the hematology of goitre an increase in the polymorphonuclear count and a decrease in the lymphocytes. In clinical hypothyroidism (myxedema) the occurrence of anemia has recently been further confirmed by Bezançon, Jacquelin and Cayla (5) and by Lisser and Anderson (6). Means, Lerman and Castle (7) have reported five cases of simultaneous occurrence of myxedema and primary anemia. They left open the question whether the association was merely coincidental.

Experimental thyroid feeding was noted by Kunde (2) to cause first an increase in the red cell count and a corresponding augmentation of the hemoglobin. If the treatment was prolonged there appeared as a secondary reaction an anemia characterized by depression in the color index and diminished size of the individual erythrocytes. Her work was based on an extensive series of rabbits, both normal and "cretin." As in her thyroidectomy experiments the blood volume was shown to have remained within the normal range. In the "cretins" but not in the normal subjects an increase in reticulocytes ranging from 4 to 10 per cent was seen to follow the thyroid feeding. In seven rabbits to which thyroid substance was fed Schermann (3) noted an increase in the red cells and the hemoglobin. In most cases the leucocytes decreased with concommitant increase in the lymphocytes, monocytes and basophiles.

Jedlowski (8) has recently reported an interesting variant of the conventional thyroid feeding experiment. He administered extract by daily injections to either pregnant or lactating mothers and studied the blood pictures in the offspring. In 26 guinea pigs treated ante partum the erythrocyte count averaged 6,150,000 as compared with 4,500,000 in control animals suckled by non-thyroidized mothers. The effect persisted only 15-20 days after which the cell count was found to be normal. In 30 rabbits that were being suckled by thyroidized mothers there was a slight increase in the red cells, a decrease in the leucocytes and a marked aug-

mentation of the reticulocytes. This latter reaction was obtained by Kunde only in rabbits initially hypothyroid. In Jedlowski's experiments, decrease in the "pseudoeosinophiles" was also noted. In the lactating series discontinuance of the thyroid treatment was followed shortly by a return of the erythrocyte count to normal but a mild leucopenia and slight lymphocytosis persisted for some time.

Rondelli and Matteis (9) administered thyroxine to 20 human subjects and noted blood changes "characteristic of vagatonia," namely, leucopenia and lymphocytosis. The results were interpreted as marking a reversion of the blood to the juvenile type as a result of the increased metabolism.

Hoskins and Sleeper administered desiccated thyroid substance for prolonged periods to 15 schizophrenic male human subjects. Of these, nine were diagnosed as suffering initially from mild (non-myxedemic) hypothyroidism, one from an undetermined endocrine deficiency and five as showing no detectable endocrine abnormality. In all but two cases there was an initial secondary anemia, the average red cell count being 4,635,000. In 13 of the cases the response to thyroid feeding was an increase of the erythrocytes, the average of the total series being raised to 5,151,000. In 11 of the cases the secondary anemia was completely corrected. The beneficial effect was not confined to the hypothyroid group hence was interpreted as non-specific; Kunde, too, in her rabbit experiments got positive effects in both normal and hypothyroid subjects. Less consistently, in nine subjects the total leucocyte count was also increased; for the total series the average was raised from 8503 to 9113. The differential lymphocyte count was increased from an average of 33.0 to 40.8 per cent. Other leucocytic elements were not significantly affected except that eosinophilia developed in four cases in two of which it was transient.

Bezançon (5) and Lisser (6) have recently added to the literature two more cases of hypothyroid subjects who reacted sharply to thyroid treatment. The initial red cell counts were, respectively, 2,600,000 and 2,736,000; after treatment the counts rose to 4,704,000 and 3,800,000.

Three recent studies of clinical "hyperthyroidism" may be mentioned. Jackson (4) concluded from observations on 600 patients that the blood picture is not significantly different from normal. There was no apparent correlation between the blood counts and the basal metabolic rate, the weight, sex, age, or clinical improvement resulting from iodine medication. On the other hand Thaddea (10) noted various characteristic departures from normality in 45 cases of "dysthyreosis" ("Basedow's disease in miniature"). Both the red cell counts and the hemoglobin values were high though a considerable proportion of immature, hemaglobin–poor erythrocytes entered into the counts. A neutropenia occurred in 18 of the cases, lymphocytosis in 29, light eosinophilia in seven and basophilia in 14. Moldawsky (11) states that by the use of supravital staining one can always demonstrate an increase in "granulofilocytes" in Basedow's dis-

case. This finding he regards as proof that stimulation of the hematopoietic tissues occurs. The finding, he states, appears early in the disease and has considerable diagnostic value. As previously suggested the variability reported in toxic goitre can perhaps be accounted for by the inclusion of different types of patients and of cases of varying degrees of severity. As Kunde demonstrated, the effect of thyroid feeding may vary depending upon chronicity and the same may be true of clinical "hyperthyroidism."

Altogether the recent literature confirms older findings that thyroid deficiency results in depression of the red cell counts and total hemaglobin. Lymphopoenia has also been reported by two observers. Thyroid feeding, on the other hand, reported to be followed by increase in the red cell counts, succeeded by a fall. An increase in reticulocytes has been noted by Knude and Jedlowski. Some observers have reported an increase and some a decrease in the total leucocytes but lymphocytosis has been commonly noted. In clinical "hyperthyroidism" recent work agrees with that of earlier investigators to the effect that the blood findings are highly variable. This variability may be provisionally ascribed to the inclusion of essentially different clinical conditions as "hyperthyroidism" and to variations in the severity of the disorder. That the thyroid hormone has an initial effect of stimulating red blood cell formation is now sufficiently established. A tendency to increase the lymphocyte counts at the expense of the polymorphoneuclear cells is also rather commonly noted but, on the whole, the effects on the leucocyte counts in general is less clearly established. It would seem evident that there is need at this juncture for the determination of the factors that modify the reactions to thyroid administration. This having been accomplished it may be possible to reconcile the now discordant evidence regarding the blood picture in thyroid diseases.

THE PRESENT STUDY

During the past five years we have been conducting a study of the etiology and treatment of schizophrenia. In the course of the investigation 107 adult male subjects have been treated for varying periods and in varying doses with thyroid substance or thyroxine.* The urine chemistry, blood chemistry, blood morphology, oxygen consumption rate, and a large series of miscellaneous physiological functions of the patients were studied at fairly frequent intervals before and during therapy.

This paper is devoted to an anlysis of the effects of thyroid medication on the blood picture. Of the total number of patients only 82 were studied sufficiently thoroughly to permit inclusion in this report. Table I presents various of the characteristics of the patients prior to treatment.

I. *The Population Studied.*

Age and Hospitalization Period: The average age of the subjects was about 30 years. The youngest was 16 and the oldest 51 years of age. Of

*Several different preparations were used. We desire to express our appreciation of cooperation of the following firms in supplying material: E. R. Squibb and Sons, Armour & Co., Parke Davis & Co., Schieffelin & Co., and Burroughs Wellcome & Co.

TABLE I

CHARACTERISTICS OF THE PATIENTS PRIOR TO TREATMENT

Variable	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation
Age (Years)	16	51	35	29.8±.59	8.05±.42	27.0%
Hospitalization Period (Years)	0.16	23	22.8	3.3±.27		
Initial Nutritional Index (%)	63	117	54	83.9±.87	11.33±.61	13.5%
Initial Basal Metabolic Rate (%)	61	119	58	82.4±.78	10.63±.55	12.9%
Initial Erythrocytes*	4,010	5,865	1,855	4,896±33	450±23	9.2%
Initial Leucocytes	4,450	20,450	16,000	10,317±254	3,420±180	33.1%
Initial Polynuclears (%)	45	88.5	43.5	62.5±.57	7.65±.40	12.2%
Initial Lymphocytes (%)	10.5	49.5	39.0	33.5±.53	7.05±.37	21.0%
Initial Eosinophiles (%)	0	14.5	14.5	2.46±.18		
Initial Transitionals (%)	0	7.0	7.0	1.06±.098		
Initial Basophiles (%)	0	4.0	4.0	.80±.06		

*Erythrocytes in thousands.

the total number 82.5 per cent fell between the ages of 20 and 40 years; 7 per cent were below and 10.5 per cent above this range. The higher ages are probably not adequately represented.

The period in hospital varied from two months to 23 years but the bulk of the patients were relatively recent arrivals; 69.5 per cent were in the group hospitalized only 0-3 years. The average period was 3.3 years. Incidentally, the mean hospital stay of schizophrenic subjects in Massachusetts State hospitals is 11 years; our group was not, therefore, entirely representative of such populations.

Nutrition and Oxygen Metabolism: As compared with the normal weights for given heights and ages compiled by the Metropolitan Life Insurance Company, our population prior to medication was on the average 16 per cent underweight. About 40 per cent of the patients were more than 20 per cent underweight, 33 per cent were 20-11 per cent underweight, and 23 per cent were of standard weight (90-110 per cent of Metropolitan standard). Four per cent were overweight. We were dealing then with a population well below the nutritional standards of the general population.

The oxygen consumption ("basal metabolic") rates before medication were also rather strikingly low. The rates are expressed as percentages of the means of the Harris-Benedict and Aub-Dubois determinations.* The lowest rate in the series was 61 per cent and the highest, 119 per cent but the majority of the patients—approximately three-fourths—had rates below 90 per cent. The mean rate was 82 per cent. This datum likewise indicates special selection in that the average oxygen consumption rate

*The rates are recorded directly as percentages of normal rather than plus or minus a given amount. Thus "61 per cent" is equivalent to "—39 per cent," as more commonly expressed.

of our larger series of 214 patients (12) was 89 per cent. This comes about from the fact that patients in the present series were chosen for thyroid medication largely on a basis of indications for its use. A low oxygen consumption rate was one of the criteria used in the selection.

TABLE II

ENDOCRINE AND PSYCHIATRIC CLASSIFICATION OF THE PATIENTS REPORTED

Initial Endocrine Diagnoses	H	P	C	S	U	M	Totals
Endocrine Deficiency	18	6	18	6	9	4	61
Indeterminate	3	2	0	0	0	0	5
Non-Endocrine	6	2	1	0	3	2	14
Undiagnosed			1			1	2
Totals	27	10	20	6	12	7	82

H = Hebephrenic. P = Paranoid. C = Catatonic. S = Simple. U = Unclassified. M = Mixed.

Endocrine and Psychiatric Diagnoses: Table II shows the endocrine and psychiatric classifications of the 82 patients prior to therapy. The incidence of endocrinopathy is higher than in our general population because of the fact that patients presenting definite endocrine "leads" received preference in selecting the group for treatment.

Of the 82 patients 61 were diagnosed as suffering from endocrine deficiency. In 15 the thyroid was the gland at fault.* The relative incidence of endocrinopathy was largest in the "Simple" group (100 per cent, but only six cases in all). Next, the "Catatonic" group showed an incidence of 90 per cent; "Unclassified" followed with 75 per cent, while the "Hebephrenic," "Paranoid," and "Mixed" groups each showed about 60 per cent endocrinopathies.

Initial Blood Picture: The samples for blood counts were taken with the patient invariably in the "basal" state between 8:00 and 9:00 A.M. Thus variation due to food, physical activity, etc., is largely excluded, and comparison of observations before, during and after therapy is on a fairly safe basis. A certain amount of uncontrolled variability, however, presumably occurred due to psychomotor tension. This could have been obviated only by sedation which, in turn, would have introduced a variable. The samples were drawn by a skilled technician who used all due care to avoid exciting the subjects. Posture also was not controlled.

The red cell counts prior to therapy (Fig. 1A) ranged from 4,010,000-5,865,000 with a mean value of 4,896,000 and a relative variation of 9 per cent. The subjects were all *adult males.* The *average* count of 4,896,000 therefore, indicates that we were dealing generally with a somewhat anemic population. We shall arbitrarity designate counts below 5,000,000 as representing secondary anemia. Using this criterion we find an incidence of 66 per cent secondary anemia in our sample. There were no significant

*The diagnostic criteria employed are discussed by Hoskins and Sleeper (13).

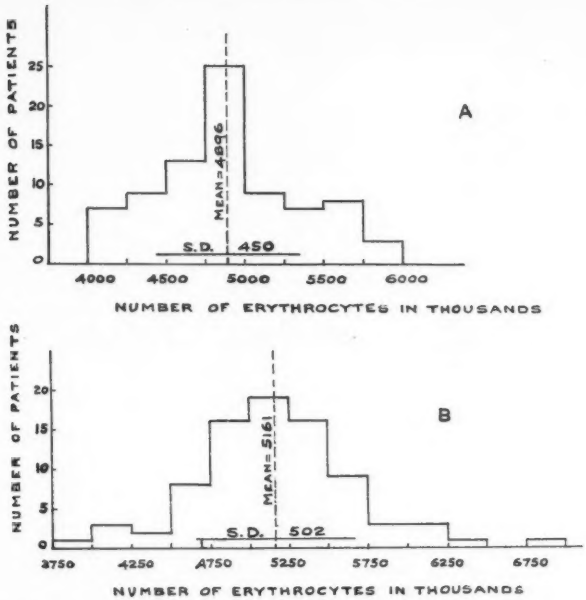

Figure 1. Distribution graphs showing red cell counts (in thousands). A, before medication; B, after medication. S. D.—Standard Deviation.

differences as to the incidence of secondary anemia in the various psychiatric sub-classes (See Table X). Since secondary anemia was one of the diagnostic criteria used in identifying "thyroid deficiency," we naturally find distinct differences by endocrine classification. Of the patients diagnosed as suffering from thyroid deficiency 80 per cent showed anemia, while in all other endocrine patients together the incidence was 59 per cent.

The initial distribution of white cell counts is shown in Fig. 2A. The mean number was 10,317, indicating a fairly high individual incidence of leukocytosis. As a matter of fact 29 per cent of the patients had counts above 10,000. The individual counts ranged from 4,450 to 20,450 cells. The relative variation was 33 per cent, that is, much higher than the variation in erythrocytes. As is well known, high leucocyte counts without

TABLE III—A
INCIDENCE OF ABNORMAL FINDINGS

	Number of Patients	Percentage of Group
Initial Secondary Anemia (Below 5,000,000)	54	66%
Initial Leukocytosis (Above 10,000)	24	29%
Initial Polynucleosis (Above 70%)	9	12%
Initial Lymphocytosis (Above 40%)	16	20%
Initial Eosinophilia (Above 5%)	7	9%

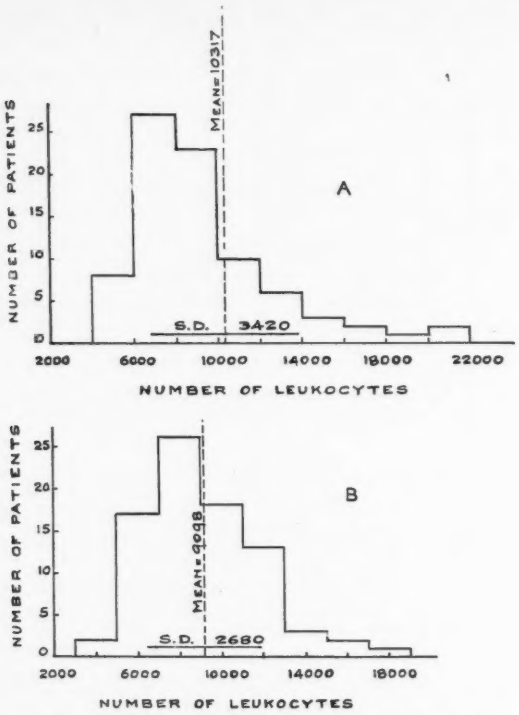

Figure 2. Distribution graphs showing leukocyte counts in all patients: A, before medication; B, after medication.

detectable cause are common in schizophrenia. In our population the blood sedimentation rates and the Schilling indices were commonly normal, indicating absence of acute hidden infection.

Coming now to the differential counts we see that the polymorphonuclear cells (Fig. 3A) ranged between 45 per cent and 88.5 per cent of the total leucocytes with a mean of 62.4 per cent, which may be designated as high normal. We designate as "polynucleosis" values of 70 per cent and above as against the usually accepted 66 per cent. This seems to be justified if we consider that the normal range of lymphocytes (small and large) is generally recognized as 25-40 per cent, and that 5 per cent may be allowed for the total of eosinophiles, basophiles, and transitionals. On this basis we had initially a 12 per cent incidence of polynucleosis.

The lymphocytes (Fig. 4A) showed a range from 10.5 to 49.5 per cent with a mean of 33 per cent. The relative variation was 21 per cent compared with 12 per cent variation in polymorphonuclear cells. Actual lymphocytosis (40 per cent and above) occurred in one-fifth of the patients. There is a certain though not very significant selection of patients as regards the item of lymphocytosis, this too, having served as a minor diag-

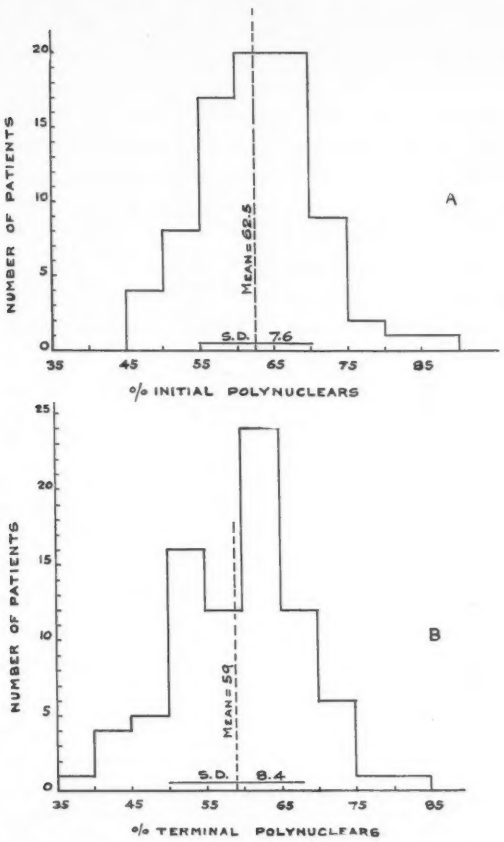

Figure 3. Distribution graphs showing percentage of polymorphonuclear leukocytes among the total leukocytes in all patients: A, before medication; B, after medication.

nostic criterion. It was taken as a general sign of endocrinopathy, however, rather than distinctively of "thyroid deficiency."*

Table III. B. shows that as would be expected, lymphocytosis occurred much more frequently in the absence of increased leukocyte counts than

TABLE III—B

INCIDENCE OF LYMPHOCYTOSIS IN RELATION TO LEUCOCYTE COUNTS

	Initial Lymphocytosis	No Initial Lymphocytosis	Totals
Initial Leukocytosis	3	21	24
No Initial Leukocytosis	13	45	58
Totals	16	66	82

*See Rowe (14).

TABLE III—C

INCIDENCE OF POLYNEUCLEOSIS IN RELATION TO LEUCOCYTE COUNTS

	Initial Polynucleosis	No Initial Polynucleosis	Totals
Initial Leukocytosis	7	17	24
No Initial Leukocytosis	2	56	58
Totals	9	73	82

in their presence, while polynucleosis (Table III. C.) was rather associated with a total increase of leukocytes. Taking now these cases of lymphocytosis and polynucleosis which occurred in association with leukocyte

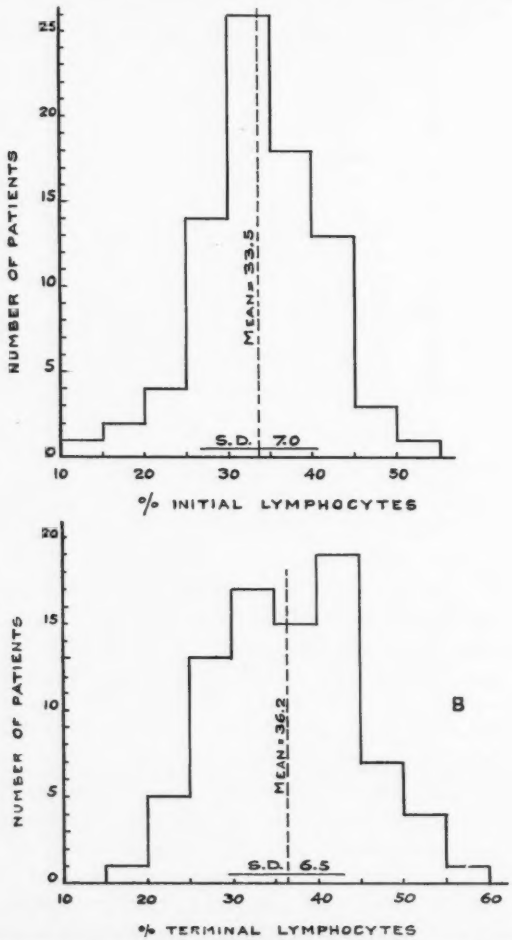

Figure 4. Distribution graphs showing percentage of lymphocytes among the total leukocytes in all patients; A, before; B, after medication.

counts lower than 10,000 we may say that the population prior to therapy showed 29 per cent absolute, and 18 per cent relative leukocytosis.

In the various patients the eosinophiles made up from 0 to 14.5 per cent of the total leucocytes, but high values were infrequent, and the mean was only 2.5 per cent. Taking Kilduffe's standard of 5 per cent as the upper limit of normality, we find an initial incidence of 9 per cent eosinophilia in our sample. We would mention that stool examination disclosed parasitosis in two of the seven cases showing eosinophilia, but in the other cases no evidence of parasites could be found.

The transitional cells ranged from 0 to 7 per cent with a mean of 1 per cent; the basophiles ranged from 0 to 4 per cent with a mean of 0.8 per cent.

Summarizing the Situation: We were dealing with a sample largely selected for endocrine "leads." The mean age of the patients was 30 years and the mean hospital stay, 3.3 years. The patients were, on an average, 16 per cent underweight, and their oxygen consumption ("basal metabolic") rate showed an average deviation of —18 points from standard. The incidence of secondary anemia was 66 per cent; of absolute leukocytosis, 29 per cent and of relative leucocytosis, 18 per cent, making a total leucocytosis of 47 per cent. Initial eosinophilia was shown by 9 per cent of the patients.

II. *Therapy—Dosage, Duration.*

Selection of Therapeutic Studies: The study under discussion was made on 82 patients. However, owing to clinical considerations, the thyroid therapy was discontinued in some cases at a given state and the patient after due rest, scheduled for some other therapy, after which he again received thyroid treatment. Also, some patients were on long visits after a given therapeutic study but, returning to the hospital, resumed treatment. Thus we had available for report a total of 120 individual studies.

The question arises, now, whether we should take the studies or the patients as the basis of our analysis. What would happen if we were to utilize all studies for the correlations? Fifty-three patients had one study only, 16 patients had two studies, nine patients had three studies, and two patients had four studies. Since there are individual reactions to therapy, the reaction type of some patients would be better represented than that of others, hence some tendencies would receive overweight. Correlation studies on that basis would be hardly valid. We are utilizing, therefore, in general, one study per patient. There are a few cases in which all studies will be considered but this will be clearly distinguished from the general procedure, and the results evaluated accordingly.

We have another point to consider; if we chose one study as representative for those patients who had multiple studies, what should be the criterion of selection? We may say that the first study is the most desirable

because it gives us the true initial conditions, or we may choose the longest study because it affords a larger series of observations. Fortunately, in the majority of cases the longest study was also the first. In not more than 15 instances did we have to take recourse to the second or third study. In these cases the first studies were so short and incomplete that they were hardly informative. In the cases in which the second or third study was used these were separated from the other studies by time intervals of four to six months. Thus the question of after-effects of the first medication period is not serious. As a matter of fact, in these cases the patients started at approximately the same physiological level which they showed initially.

TABLE IV
DOSAGES AND DURATION OF TREATMENTS

Distribution	Minimum	Maximum	Range	Mean
Average Daily Dosage (Mgm. Thyroxine)	0.6	14.5	13.9	3.88
Total Dosage (Mgm. Thyroxine)	66	4522	4456.4	970
Total Medication Period (Days)	31	923	892	251
Number of Days from Beginning Medication to First Observation	6	177	171	73
Dosage (Mgm.) from Beginning Medication to First Observation	7	885	878	271

The Dosage: Since both desiccated thyroid substance and thyroxine were used, it is necessary to have a common basis for expressing the dosages of the two medicaments. Treating the data separately would result in samples too small for satisfactory statistical treatment. There are various thyroid-thyroxine equivalents mentioned in the literature but in general they are not adequately supported by chemical or other evidence. We adopted Squibb's formula according to which one grain of thyroid equals 0.6 mgm. of thyroxine. Conversely 1 mgm. of thyroxine is the equivalent of approximately 1.7 grains of thyroid. We were not entirely arbitrary in the selection since this formula yielded for thyroid such values as oc-

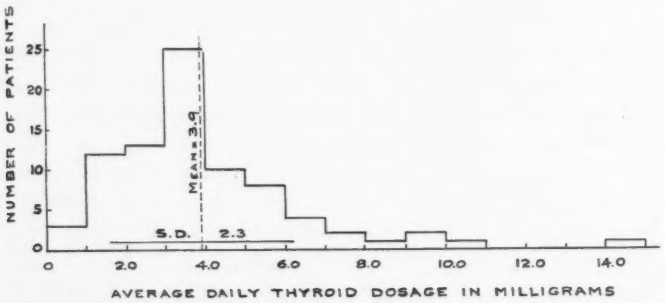

Figure 5. Distribution graph showing the average daily dosages in all patients. The dosages are expressed in mgm. of thyroxine. (Equivalent used; 0.6 mgm. thyroxine equals 1 grain desiccated thyroid).

curred in actual thyroxine therapy, while the other equivalents resulted in values well out of line. In any case the results of correlation studies on the data are not significantly affected by the degree of validity of this equivalent, since our object is to demonstrate trends rather than to establish exact mathematical relationships.

Distribution of Dosages and Medication Periods: Fig. 5 shows graphically the numbers of patients receiving each of various average dosages. Similarly, Fig. 6 indicates the total dosage received at the last day of the

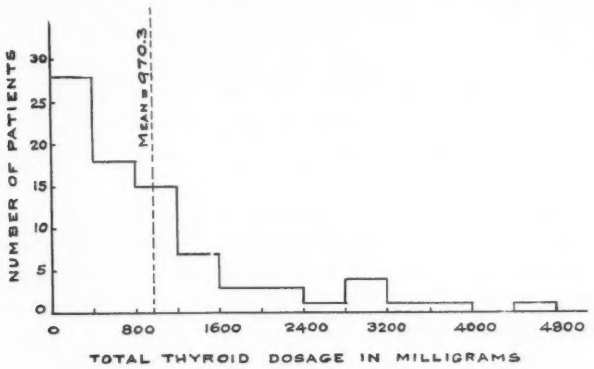

Figure 6. Distribution graph showing the total amount of thyroid (mgm. thyroxine) administered per capita to all patients. (One grain thyroid = 0.6 mgm. thyroxine).

therapeutic period. These distributions relate to the 82 studies utilized in the correlations. The lowest average daily dosage administered was 0.6 mgm. and the highest, 14.5; the average dosage for the entire series of patients was 3.9 mgm. (6.5 grains in terms of desiccated thyroid). Average dosages above 6 mgm. per day were infrequent. Not more than 13 per cent of the patients received larger amounts than that, and only 6 per cent received dosages above 8 mgm. It should be noted that the mean (3.9 mgm.) coincided approximately with the most frequent value (mode). Average dosages of 3-4 mgm. were administered to 30 per cent of the patients.

The cumulative dosages at the end of the therapeutic periods ranged from 66 to 4522 mgm. with a mean of 970 mgm. However, not more than 17 per cent of the patients received total dosages above 1600 mgm. We have thus a wide range for correlation studies, although, for obvious reasons, the high dosages are sparsely represented.

The Therapeutic Periods: As shown by Fig. 7 the duration of treatment varied considerably in the different cases. The mean period was 251 days or somewhat over eight months. Periods of 50-350 days are fairly equally distributed around this mean. About 12 per cent of the patients were treated as long as 400-923 days.

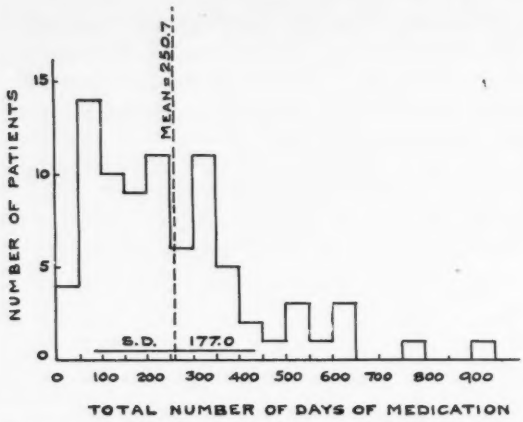

Figure 7. Distribution graph showing the duration of treatment in all patients.

Considering the range of the average daily dosage and the range of the therapeutic periods together, all kinds of conditions are represented: there are short periods with high and low dosages, and long periods with high and low dosages. From this standpoint, at least, we have ideal conditions for correlation purposes.

Intervals Between Observations: A great many of the possibilities of statistical analysis depend on the frequency of observations and the time elapsing between consecutive observations. There were available in most cases at least four determinations during the therapeutic period.

From Fig. 8 it can be seen that the first observation was made anywhere between a few days and 180 days after the beginning of medication. To be exact, the range was 6-177 days with a mean of 73 days, the

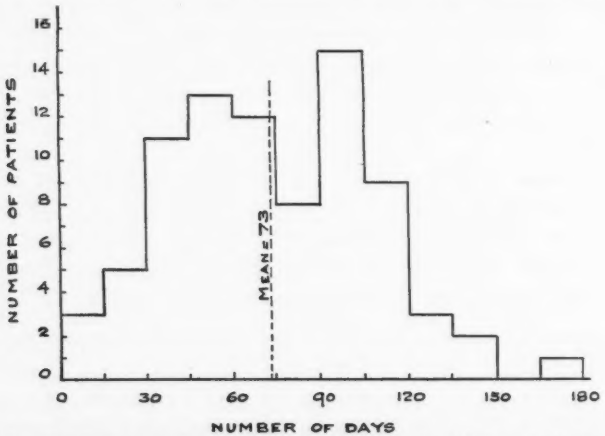

Figure 8. Distribution graph showing number of days elapsed from beginning of medication to study of blood picture (all patients).

bulk of the first observations being made between 30 and 120 days from the beginning of treatment.

Similarly, the variation in total dosage received at the time of the first observation shows a wide range: 7-885 mgm. with a mean of 271 mgm. (Fig. 9.).

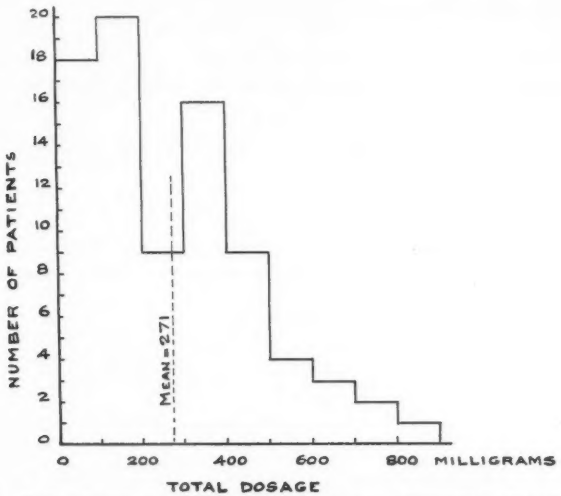

Figure 9. Total amount of thyroid (expressed as mgm. thyroxine) administered to each patient at the time of study of blood picture. (Equivalent: 0.6 mgm. thyroxine = 1 grain desiccated thyroid).

In case of a very large sample, say 1000 patients, each of these class intervals would include sufficient individuals to warrant the assumption that all reaction types would be proportionately represented and we should be in position to utilize the means of the red blood counts or any other variable for each of these arrays as characterizing the reaction to a given number of days or a given thyroid dosage. With a limited sample, however, the unsystematic procedure that was followed (for clinical reasons) is a definite drawback, and we have great difficulties in estimating the nature of diphasic reactions. This must be kept definitely in mind in considering the analysis of the results.

III. *Therapeutic Results.*

The Evaluation of Results: Previous sections have included a description of the pre-therapeutic status of the patients, and statements as to the dosages and medication periods. The results of the therapy as reflected in the changes in blood morphology may now be discussed. Since the ultimate object of therapy was mental improvement of the patients, even though it was hoped to achieve this through normalization of the organic functions, the therapeutic regimen was governed more by the psychiatric than the organic picture. Thus a therapeutic study was regarded as completed either when definite mental improvement had been noted

or when there seemed to be no hope to achieve such improvement through the given therapy. Changes in the blood picture may then not be evaluated in the same way as would be done in case the object of the thyroid medication were primarily to cure the secondary anemia. Nevertheless, the results may be indicative of therapeutic possibilities and may open up a new vista of experimental procedures.

TABLE V—A

CHANGES IN THE ERYTHROCYTE COUNTS DURING THERAPY

			Initially High (Above 5,000,000)	Initially Low (Below 5,000,000)	Totals
High Dosage..... (Above 500 mgms.)	Short Period..... (Less than 200 days)	Increase	8	9	17
		Decrease	9	2	11
	Long Period..... (More than 200 days)	Increase	2	16	18
		Decrease	7	1	8
Low Dosage..... (Below 500 mgms.)	Short Period..... (Less than 200 days)	Increase	10	26	36
		Decrease	16	5	21
	Long Period..... (More than 200 days)	Increase	0	7	7
		Decrease	2	0	2
		Totals	54	66	120

Effect on the Blood Picture in General: Tables V A and V B afford a rough picture of the effect of thyroid feeding on the red and white cell counts. All of the 120 studies are considered in this table. "Increase" and "decrease" relate here to changes of any degree without discrimination. "High" and "low" dosage as well as "long" and "short" medication periods are of course vague and arbitrary standards. Naturally, we shall later become more specific about these variables, but this tabulation, in spite of its obvious defects, gives a compact picture of the results. The roughness of the table is largely outweighed by the great consistency shown by certain aspects of it.

It is immediately apparent that the direction of change was much more definite when the *red cell* count was low than when it was high in the beginning. With extraordinary consistency we see increases in the red blood counts in the patients at first showing secondary anemia, and this increase appears in all combination of duration of therapy and amount of dosage. Of all the 66 studies which start with secondary anemia, only eight studies, or roughly 12 per cent, showed a decrease in erythrocytes, while in 58 studies, or roughly 88 per cent, an increase was noted.

On the other hand, when the red cell count was initially high (above 5,000,000) decreases were more frequent than increases, though this decreasing tendency was not so consistent as was the increasing tendency in the initially low counts. Of the 55 studies with early high counts, 20 studies, or approximately 36 per cent, showed an increase, and 35 studies, or roughly 64 per cent showed a decrease in erythrocytes.

It appears then that when we wish to come down to the specific effect of thyroid substance on the red cell count, that is, when we correlate actual dosage with the number of erythrocytes, we cannot take the population as a whole; the contrary tendencies in the two groups of initially high and initially low counts would cancel each other to greater or less degree. It is fully justified to give the question this form: what is the correlation between the amount of thyroid substance ingested and the number of erythrocytes in patients who were anemic before treatment?

TABLE V—B

CHANGES IN THE LEUKOCYTE COUNTS DURING THERAPY

			Initially High (Above 7,500)	Initially Low (7,500 and Below)	Totals
High Dosage..... (Above 500 mgms.)	Short Period..... (Less than 200 days)	Increase	8	9	17
		Decrease	10	1	11
	Long Period..... (More than 200 days)	Increase	9	6	15
		Decrease	6	5	11
Low Dosage..... (Below 500 mgms.)	Short Period..... (Less than 200 days)	Increase	16	12	28
		Decrease	27	2	29
	Long Period..... (More than 200 days)	Increase	4	2	6
		Decrease	2	1	3
		Totals	82	38	120

The figures relate to the number of studies, not to the number of patients.

As to the behavior of the *leukocytes,* Table V B affords some information. There is a great but hardly avoidable weakness in this table, namely, the terms "high" and "low" counts do not distinguish between normal and pathological conditions, but are somewhat arbitrary. The reason is that while white counts of 10,000 cells constitute the pathological condition of leukocytosis, one can hardly speak of low values simply because the count is below 10,000. We may designate counts between 7500 and 10,000 as high normal, and counts between 5,000 and 7500 as low normal. We arrive on this basis much nearer to the true behavior of the leukocytes under thyroid medication than if we were to take the conventional limit of pathological conditions as the division line.

It will be noted that, compared with the erythrocytes, the proportion of initially low to initially high values is reversed in the leukocytes. While in case of the red cells the low counts were predominant, in the white cells the high counts prevailed. Though in general the initially low values tended to increase during therapy, while the high counts tended to fall, the consistency of these trends is much less than the consistency shown in the behavior of erythrocytes. Of the 38 studies with early "low" counts, nine studies, or about 24 per cent showed a decrease while 76 per cent showed an increase. In the case of initially "high" counts (82 studies) about 45 per cent showed an increase, and 55 per cent showed a decrease.

While the foregoing presentation brings out certain general tendencies, it is not informative as to the significance of the changes; that is, it fails to indicate whether the incidence of secondary anemia has been decreased or the incidence of leukocytosis increased. The data may now be presented more specifically.

TABLE VI
BLOOD CELL COUNTS AT CLOSE OF MEDICATION

Variable	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation
*Erythrocytes.....	3,860	6,840	2,980	5,161±37	5,025±26	9.7%
Leucocytes.....	3,650	18,800	15,150	9,098±200	2,680±141	29.5%
Polynuclears.....	36.5	82.0	45.5	59.0±.63	8.45±.45	14.3%
Lymphocytes.....	15	59	44	36.2±.48	6.5±.34	17.9%
Eosinophiles.....	0	13.25	13.25	2.3±.17		
Transitionals.....	0	13.25	13.25	1.71±.14		
Basophiles.....	0	5.0	5.0	.61±.05		

*Erythrocytes in thousands.

Changes in Red Cell Counts: Table VI presents various data regarding the cell counts at the end of the medication periods. Comparison of these values with those of Table I brings out such changes as took place.

Fig. 1 A and B gives us a comparison of the distribution of erythrocytes before and at the close of thyroid therapy. The average of 4,896,000 increased to 5,161,000 during medication. The difference was 265,000± 49,579. This is statistically a highly significant difference. Too, we must consider that the shape of the whole distribution changed. Before therapy there was a larger area at the left of the 5,000,000 line, while after therapy the larger area was to the right of that line. It should be noted that the relative variation did not change; the coefficient of variation in both samples is roughly 9 per cent. Naturally, significant shifts in the number of erythrocytes may occur in the absence of therapy. We have, fortunately, determinations during purely observational periods, and we find that in the absence of treatment there was a tendency over fairly long periods toward lower red cell counts. During an interval of approximately three months the mean changed from 4,890,000±42,000 to 4,372,000±39,000, that is, on the average, a loss of 518,000±57,000 red blood cells occurred in these untreated patients. In view of this fact the above mentioned gain during therapy receives additional significance.

It will be recalled that Table V A showed that the changes were of different direction according to whether the initial values were high or low. Therefore, we should treat here the initially anemic population separately. Fig. 10A shows the distribution of erythrocytes in patients with initial secondary anemia (below 5,000,000 cells) while Fig. 10B shows the distribution of erythrocytes in the same population after therapy. These

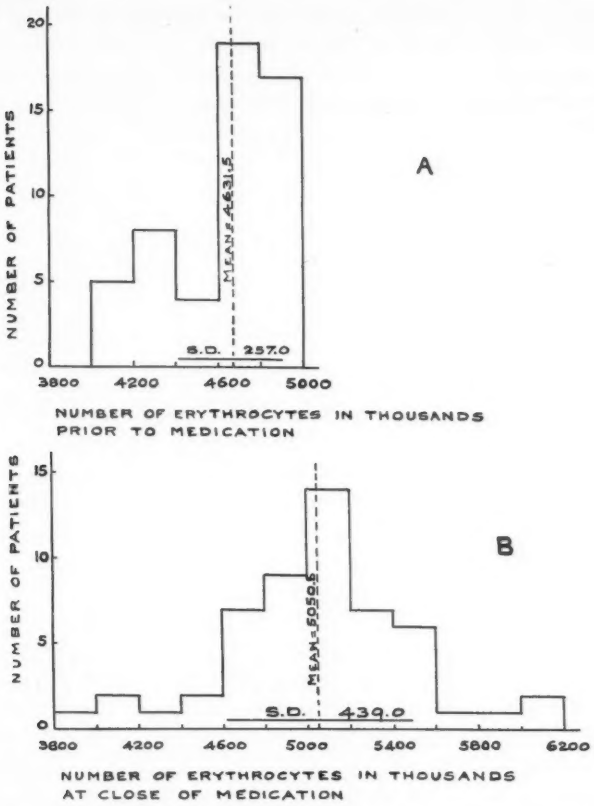

Figure 10. Distribution graph showing the number of red cells in each of 52 patients initially anemic; A, before treatment; B, after thyroid treatment.

diagrams describe better than words what had happened during treatment. The mean was raised from 4,631,500 to 5,050,500 and about 58 per cent of the patients passed the 5,000,000 line. As earlier stated, there is a certain tendency for abnormal counts to normalize irrespective of medication. How much did this tendency figure in the changes coincident with treatment? There were available in our series enough multiple determinations in anemic patients without medication for a fairly satisfactory answer to the question. It was found that 71 per cent of the subjects that were below the 5,000,000 line remained there. Although the mean was about 120,000 cells higher after the second observation period, owing to a few exceptionally high increases, the majority of this anemic population shifted to even lower values than they had in the first observation period. Relatively little discounting of the apparent effect of the thyroid medication on the score of "spontaneous normalization" is indicated.

It is a matter of special interest that red cells were usually higher at some stage during treatment than at the end. Only in subjects who for one reason or other had relatively short courses of treatment was the improvement continued uninterruptedly to the end. Fig. 11 shows the amount

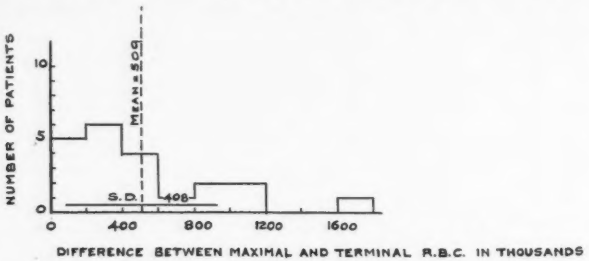

Figure 11. Distribution graph showing the falling off in the red cell count during the progress of the thyroid treatment in 52 patients initially anemic.

of falling off from the highest point reached in the various cases. The decreases ran as high individually as 1,600,000 cells. The most frequent difference was between 200,000 and 400,000 cells. The average falling off for the whole series was 509,000 cells. In the administration of gland therapy the possibility always has to be considered that any given preparation may have a diphasic effect on one or another function (15). Thus adrenalin in one dosage lowers blood pressure, in another dosage, raises it. The first evidence of a diphasic reaction encountered in our thyroid studies was in the hematopoietic effect just discussed. A practical point of interest is that had the thyroid been used purely as a cure for secondary anemia, the results could have been better than those achieved by us, whose aim was mental improvement of the patients. Obviously the treatment would have been readjusted at the point at which the red cell counts began to fall off.

As shown in Fig. 12 the maximum red cell count occurred, on the average, at the end of 166 days. There was a wide range in various cases but in most instances it fell between 75 and 175 days. If we compare the mean

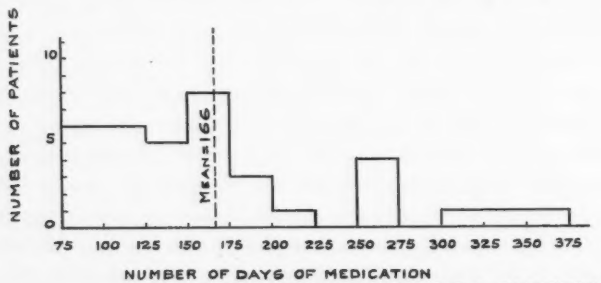

Figure 12. Distribution graph showing the number of days after the beginning of thyroid treatment at which the maximal increase of erythrocytes occurred. (Based on study of 52 patients initially anemic).

period of maximum efficacy with the mean duration of the entire therapeutic periods, which was 250 days, we get a clearer concept of the diphasic reaction.

No less interesting than the optimal period of medication is the optimal total dosage. The highest cell count was achieved in the various cases with dosages ranging up to 1600 mgm. (Fig. 13). The best effect

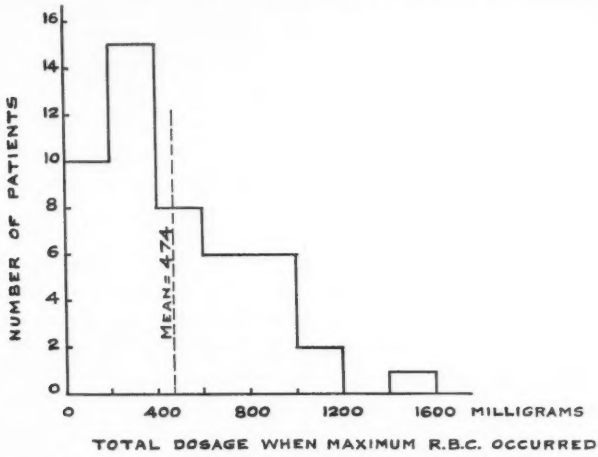

Figure 13. Distribution graph showing the total dosage of thyroid received when the erythropoietic effect was at maximal height. (Based on study of 52 patients initially anemic. Dosage expressed in mgm. thyroxine, of which 0.6 mgm. = 1 grain desiccated thyroid).

was obtained, on the average, with total dosage of 474 mgm. This is less than half the mean total dosage, 970 mgm., that had been received by the patients at the close of the medication period.

The Changes in the Leucocyte Counts: The changes in the total leucocyte counts following medication were relatively insignificant and will not be reported in detail. Suffice it to state that the average count before treatment was 10,317 cells with a standard deviation of 3420. The range in the series as a whole was from 4000 to 22000. After thyroid treatment the average white count had dropped to 9098 cells with standard deviation of 2680 and range from 3000 to 18000. Thus the average count had dropped about 1200 cells. (The actual difference was 1219 ± 323). The lowering of the mean was due largely to the disappearance of a few notably high counts after therapy and the appearance of two or three extremely low values.

As regards the differential counts the thyroid treatment was without statistically significant effect on the proportions of polymorphonuclear leucocytes, eosinophile, basophile or transitional cells. The mean values before and after treatment were as shown in Tables I and VI. Only in case of the lymphocytes was a significant difference seen. Before treatment the lymphocytes constituted 33.5 per cent of the total white cells. After treat-

ment the proportion was 36.2. The difference was but 2.7 ± 0.71 per cent but this is regarded as statistically valid. The significance of the changes is discussed in a later section.

TABLE VII

CHANGES IN CELL COUNTS DURING TREATMENT

	Prior to Medication		During Medication		At End of Medication	
	No. of Patients		No. of Patients		No. of Patients	
Secondary Anemia	54	66%	50	61%	30	37%
Leukocytosis	24	29%	45	55%	31	38%
Polynucleosis	9	11%	23	28%	9	11%
Lymphocytosis	16	20%	41	50%	27	33%
Eosinophilia	7	9%	10	12%	8	10%

Incidence of Abnormal Counts Before and After Therapy: Table VII shows that while the incidence of secondary anemia had dropped to a marked extent at the close of medication, the incidence of abnormally high leukocyte counts had generally increased by the conclusion of therapy.

In case of the leukocytes, polymorphonuclears, and lymphocytes we have here again some evidence of diphasic reactions. In these three variables the incidence of pathological excesses rises remarkably during medication in turn to fall off at the close of the treatment. The incidence of polymorphonucleosis, in spite of a marked increase during medication, falls back to the initial level. Leukocytosis and lymphocytosis, however, are terminally at a higher level than initially, although a good deal below the level which they show during therapy. In eosinophilia, too, this trend is apparent but is only slightly marked, and gains significance only through its coincidence with the trends shown by the other cells.

Table VIII gives the initial and terminal incidence of secondary anemia and leukocytosis by sub-classes of schizophrenia. Aside from

TABLE VIII

EFFECTS OF THYROID THERAPY ON ANEMIA AND LEUKOCYTOSIS BY SUB-CLASSES OF PATIENTS

Initial Psychiatric Diagnosis	Total No.	Patients Showing Secondary Anemia				Patients Showing Leukocytosis			
		Initially		Terminally		Initially		Terminally	
		No.	%	No.	%	No.	%	No.	%
Hebephrenic	27	18	67	9	33	6	22	8	30
Paranoid	10	7	70	5	50	2	20	1	10
Catatonic	20	13	65	6	30	8	40	14	70
Simple	6	3	50	1	17	1	17	2	33
Unclassified	12	8	67	6	50	5	42	1	8
Mixed	7	5	71	1	14	2	30	3	42

technical psychiatric interest the table is of value in affording a check on consistency of the data. It is axiomatic in statistical science that if a given tendency is consistently maintained when the mass of data is divided into sub-groups the mass tendency is strongly validated.

It is seen that the incidence of secondary anemia decreased in all of the sub-classes. The decrease was least in the case of paranoid and the "unclassified" patients. These two groups are likewise set off from the rest as regards the behavior of the leukocytes. In the columns relating to leukocytosis it is seen that in all classes, save the paranoid and "unclassified," the incidence of leukocytosis increased during medication. These two groups, however, show a rather marked drop. The fact that they distinguish themselves in behavior in secondary anemia as well as in leukocytosis, confirms us in attaching some significance to the differences in percentages, despite the relatively small number of cases in each group.

Table IX brings out the influence of initial endocrine status on the outcome of treatment.

TABLE IX

EFFECTS OF TREATMENT ON SECONDARY ANEMIA BY ENDOCRINE SUB-CLASSES

Initial Endocrine Diagnosis	Total Number of Cases	Incidence of Secondary Anemia			
		Initially		Terminally	
		No.	%	No.	%
Thyroid Deficiency	15	12	80	4	27
Other Endocrine Deficiency	46	27	59	10	22
Indeterminate	5	4	80	2	40
Non-Endocrine	14	10	71	4	29
Undiagnosed	2	1	50	0	0

Apparently patients with definite thyroid deficiency responded in greater degree to thyroid therapy than did the other endocrine groups. However, the non-endocrine patients were not far off from the thyroid cases in their response hence probably not much significance attaches to the difference between thyroid and other endocrine patients. The numbers involved in the various groups are too small to justify final conclusions but the results as they stand suggest either that the effect of thyroid treatment is non-specific or that the initial diagnoses were faulty.

CORRELATIONS

Erythrocytes: We have pointed out that individuals with an initially high number of erythrocytes in a measure react to therapy in the opposite way from individuals with an initial anemia hence in correlation studies the effects would tend to cancel out. For correlation purpose therefore, the anemic population is treated separately. The sample is thus reduced to 52 individuals.

It would be highly interesting to follow up the reaction at each stage of therapy but owing to reasons previously discussed this is not feasible. We selected as a basis of discussion, therefore, the difference between initial and terminal values; the difference between initial and maximal values; and the difference between maximal and terminal values.

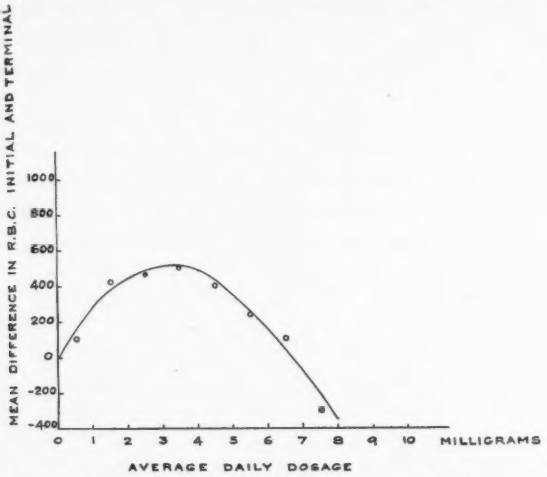

Figure 14. Graph showing the final average gain or loss in erythrocytes in relation to dosage. (Based on study of 52 patients initially anemic. Dosage expressed in mgm. thyroxine, of which 0.6 mgm.=1 grain of desiccated thyroid. R. B. C. expressed in thousands).

Figure 14 shows the relationship between the average daily thyroid dosage and change in the final red cell count as compared with that at the beginning. The plotted points are the means of all observations at each level of dosage. The solid line is a free-hand curve and does not pretend to an exact relationship, but is put in only to emphasize the direction. The reason for this will be discussed later. The relationship is clearly curvilinear; that is, for a constant rate of change in dosage, the rate of change in erythrocytes gained is not constant. The gain in erythrocytes rises to an optimum at average daily dosages between 3 and 4 mgm. of thyroxine (5-7 grains of thyroid). After that dosage the gain decreases and, beginning at about 7 mgm. per day, the gain changes into a loss. We had a few observations at dosages above 10 mgm. and in these there appeared again a rising tendency. However, observations in these higher ranges were so scanty that we thought it advisable to leave them out. It does not stand against reason that such polyphasic reaction actually should occur. Such augmented counts as were seen at the end were tentatively regarded, however, as artifactual, due to emotional hyperglobulia.

While the relationship between average dosage and final erythropoietic effect is definitely curvilinear, the relationship between average dosages and highest gain in red cells is linear (Fig. 15). That is, the higher the dosage, the greater the difference between initial and maximal erythrocytes at-

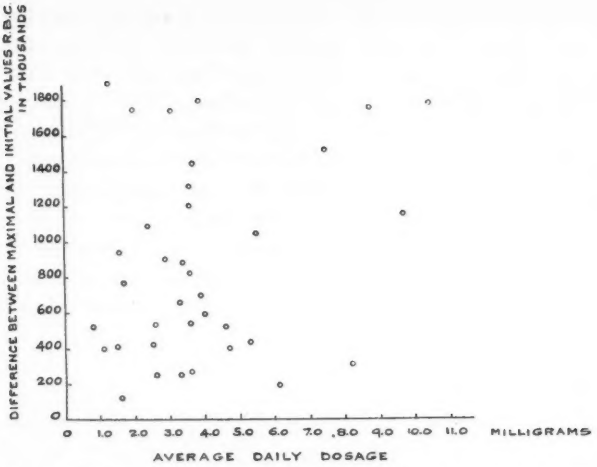

Figure 15. Scatter graph showing the relationship between dosage and maximal effect obtained in 52 patients initially anemic. Dosage in mgm. thyroxine. R. B. C. expressed in thousands.

tained during medication. The coefficient of correlation is 0.25 ± 0.087; that is to say, not more than about 4 per cent of the variation in the maxima is accounted for by the variation of dosage (not taking interfering variables into consideration).

Now we have seen before that after the maximum number of erythrocytes has been reached this high level is not maintained, but that the number decreases towards the end of the therapeutic period. Nevertheless it finishes at a higher level than the initial count. Is there any relationship exhibited by the differences between the greatest and the final effects? This relationship is represented in Fig. 16. It is markedly linear and positive, and yields a correlation coefficient of 0.54 ± 0.066. The falling off, then, is proportional to the previous gain. The variation in

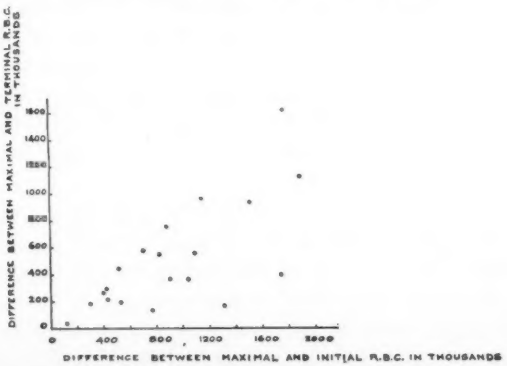

Figure 16. Scatter graph showing the relationship between maximal erythropoietic effect and the decline reached. R. B. C. expressed in thousands.

the difference between maximal and initial red blood counts covers about 16 per cent of the variation in the difference between maximal and terminal red cell counts. This again is to be understood as obtaining without consideration of the compensating factors. In other words, the more we whip up the number of erythrocytes through thyroid feeding, the greater will be the drop towards the end. Thus we can reconcile the apparent paradox that the relationship between dosage and end result is parabolic, but between dosage and maximum is linear.

Further, we may take into consideration the effect of the average daily dosage on the falling off between the highest and the final cell counts. This relationship, which is definitely curvilinear, is given in Fig. 17. It

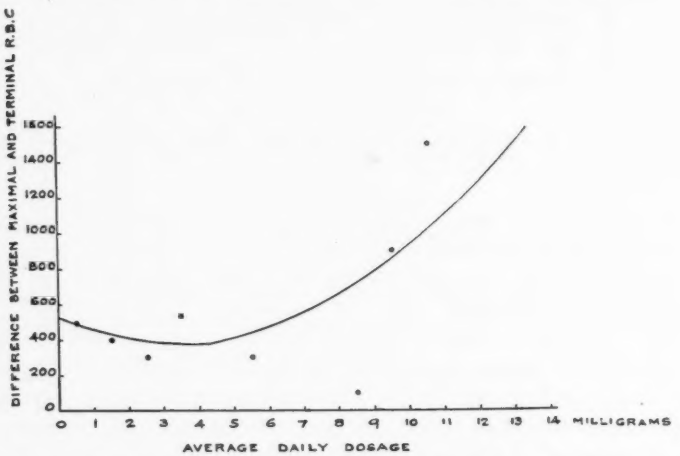

Figure 17. Graph showing the relationship between dosage and decline of red cell count after the maximum was reached. R. B. C. expressed in thousands.

appears that within the range of a few tenths to about 2.5 mgm. per day, the higher the dosage the less the difference. Up to about 5 mgm. the effect remains about stationary and above 5 mgm., the difference increases with the dosage. This relationship shows that to obtain the most lasting effect from prolonged thyroid treatment the medication should range between 2.4 and 5 mgm. thyroxine or 4 and 8 grains of thyroid a day. However, to gain the maximal effect without reference to subsequent falling off, larger doses are indicated.

The correlation ratio for the relationship of the average dosage to the final gain in erythrocytes was not more than 0.30 ± 0.084. In view of the smoothness shown in the trend of the means, we should expect a higher correlation. However, the scatter around these points is large. The consistency of the trend shows that there may be more to this relationship than the correlation ratio indicates. As a matter of fact there are a number of variables which regulate the effect of the dosage on the number of

erythrocytes, and the variation of these factors accounts for the scatter around the means plotted in Fig. 14.

Significant as this relationship may be as an expression of a general law when it comes to the selection of dosage for the individual patients the influence of certain factors other than dosage must be taken into account. This is the reason why we have not fitted the proper parabola to the means, and have not given an equation, but were satisfied with a free-hand curve giving the approximate direction only.

Certain of the other significant variables that influence the hematopoietic reactions may now be considered. *Age* was found to have a negative effect; i. e., the younger the patient the greater was his response. Likewise there was a slight influence of age on the degree of anemia he showed before medication. Correlating the age versus the initial red cell counts we obtained an insignificant negative correlation of -0.18 ± 0.7 but the correlation between the age and the extent of the increase obtained was -0.43 ± 0.075 (Fig. 18). The correlation is not high but it is definite and sufficiently marked to be considered in a therapeutic program.

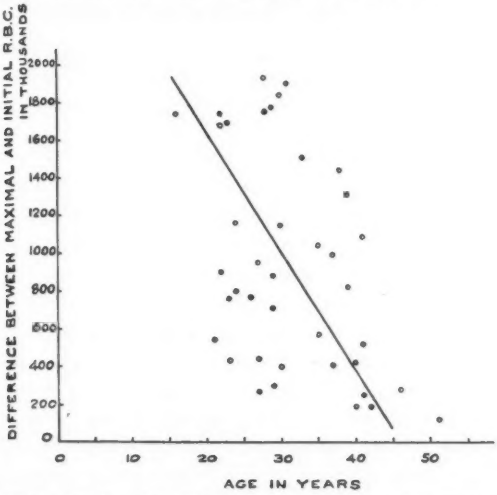

Figure 18. Graph showing the relationship between age and maximal erythropoietic effect of thyroid administration.

Next we may consider the *nutritional status* of the patients (expressed in percentage of "normal" as previously defined). Again we found, against expectation, a low correlation ($0.25 \pm .08$) between the nutrition and red cell counts but a marked relationship between the initial nutritional values and the erythropoietic effect as shown at the end of the medication period (Fig. 19). The relationship is clearly parabolic. The correlation ratio is 0.45 ± 0.074. The curve indicates that the patients with very low initial nutritional values (60 to 70 per cent of "normal" weight) do not respond so well to thyroid medication as patients with initial values between 80

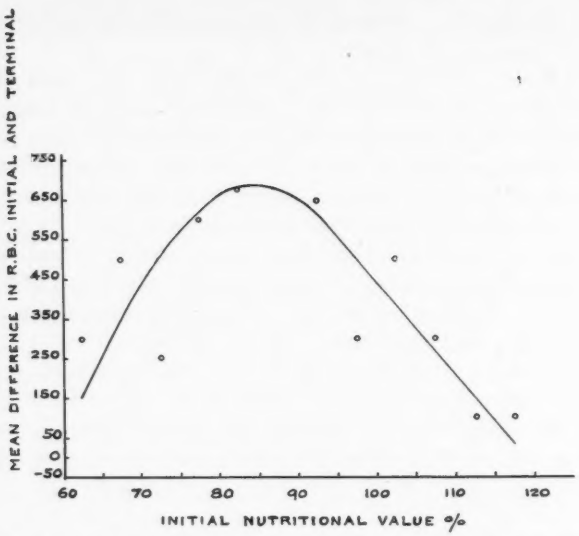

Figure 19. Graph showing relationship between the nutritional status of the patient at the beginning of thyroid treatment and the final erythropoietic effect obtained. "Nutrition" expressed as percentage of patient's weight to that of the "average patient" of his height and age. R. B. C. expressed in thousands.

and 90 per cent. These latter are most responsive to the medication. Patients who were initially of standard weight or overweight responded again less and less the higher the initial nutritional index. It may be mentioned in this connection that there is co-variation between the therapeutic effect on weight and on the red cell count. Figure 20 shows that the greater the effect of the medication on the red cell count the greater also is the effect on the patient's nutrition. The correlation is 0.42 ± 0.075. As to why malnutrition should interfere with the hematopoietic response to thyroid one can only speculate. The suggestion is obvious that the low body weights are due to some deep-seated metabolic peculiarity. It is definitely not due in our patients to under consumption of food. Their total urinary nitrogen averages about 10 gm. and they eat suitable proportions of fat and carbohydrate material.

Lastly we would mention the initial *oxygen consumption* ("basal metabolic") rate, as a factor determining the outcome of therapy. Figure 21 shows a positive relationship of moderate degree. The correlation coefficient was 0.31 ± 0.084. Generally, then, with higher initial oxygen metabolic rates the results secured are slightly better. It must be considered, however, that the initial metabolic rates show only a few readings above 100 per cent; it may be assumed that if we had a higher range the relationship would be curvilinear. As a matter of fact the two or three scattered readings in the range between 100 and 200 per cent actually suggest this. This datum, too, suggests that the effect of thyroid medication on the red

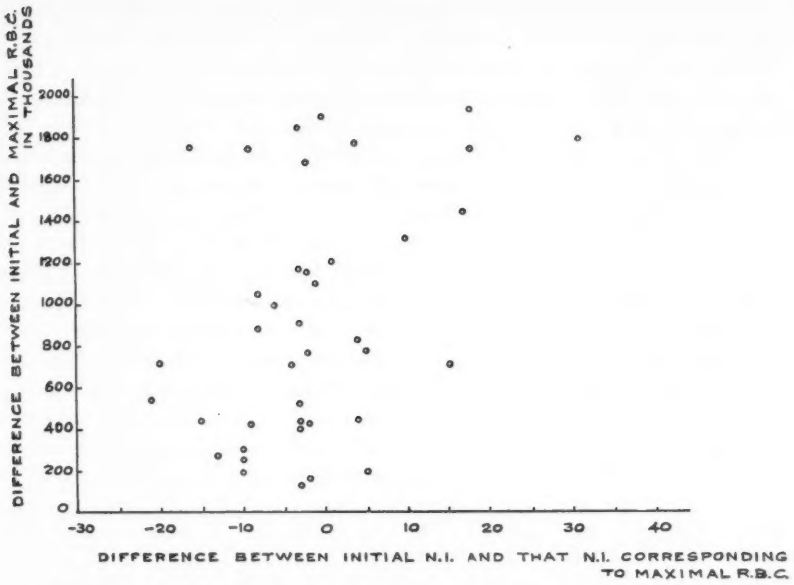

Figure 20. Graph showing the relationship between gain in weight and increase in red cell counts under thyroid treatment.

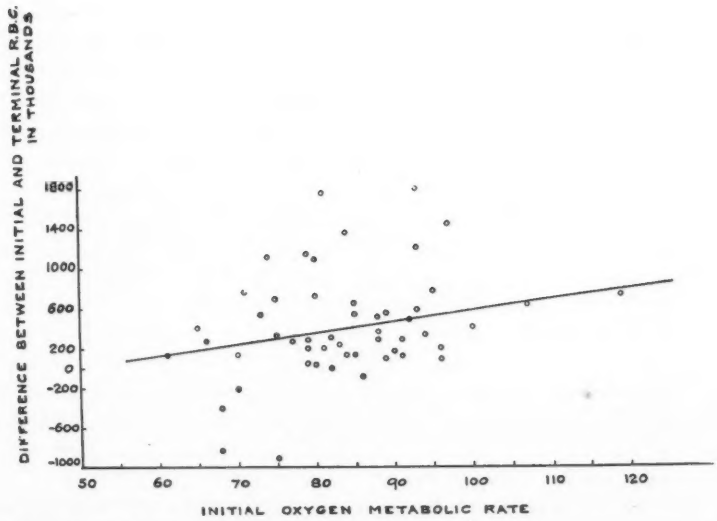

Figure 21. Graph showing the relationship between the initial oxygen consumption ("basal metabolic") rate and the final erythropoietic effect of thyroid treatment. Oxygen consumption rate expressed directly as percentage of standard "normal."

cell counts is not specific. Depression of the basal metabolic rate is a cardinal sign of thyroid deficiency. It would be supposed therefore, that the correlation just mentioned would be positive rather than negative were the effect specific. We are probably dealing here with another aspect of the peculiarity discussed in connection with "nutrition."

We found, then, three factors—age, nutritional status, and oxygen consumption rates—which more or less govern the outcome of therapy as far as anemia is concerned. These must all be taken into account in considering the effect of dosage. Naturally, it would be possible to determine the net relationship between the dosage and response by keeping all other variables constant. The method of partial correlation ratios (not partial correlation coefficients, since we are dealing mostly with curvilinear correlations) would permit of such an estimate. We are refraining, however, from the use of this method on account of the limited number of observations at our disposal. Multiple regression equations, that is, equations estimating from a number of independent variables the value of a dependent variable, should be based on a large number of observations.

White Cell Counts: As previously indicated, the effect of thyroid medication on the leukocytes was less marked than the effect on the erythrocytes. We found very loose relationships between leukocytes in general and the variables treated above. The relationships were somewhat more definite as regards the differential counts. Suffice it to state that the relative proportion of lymphocytes was generally increased by thyroid treatment. The correlation ratio was 0.28 ± 0.85. The definite lymphocytosis evoked by the higher dosages is a confirmation of the findings of Rowe (14) and others that endocrine anomalies are generally marked by this phenomenon. Our higher dosages probably represent a state of true hyperthyroidism. By the same token the effect should be diphasic for such of our patients as passed from hypothyroidism to hyperthyroidism. Indeed such an effect is suggested but the data are not sufficiently numerous to justify partialing out the relationship of hypothyroidism as such to the lymphocytic reaction. The increase of the proportion of lymphocytes was at the expense of the polymorphonuclear cells. The correlation ratio between this effect and dosage was 0.30 ± 0.084. The polymorphonuclear cells increased with increasing dosages up to a total of 800 mgm., and after that showed a sharp decline with increasing dosages.

DISCUSSION

The foregoing report is offered as representing a biometric study in a field in which, so far as we are informed, formal statistical methodology has not hitherto been employed. From the study has emerged certain relationships not previously recognized.

It must be emphasized that the observations were made on psychotic patients. Subjects of schizophrenia present numerous deviations from physiological normality. In particular, they frequently show high toler-

ance for thyroid substance (13). It is probable, therefore, that while the general laws determining the effects of thyroid medication are equally applicable to psychotic and non-psychotic subjects, our results should not be transferred to the latter, dose for dose. Allowance should be made for the tolerance factor.

One variable that was not directly controlled is the possible dilution factor. Obviously, dehydration of the blood would give an artifactual increase in the cell counts, whereas hydremia would lower them. Studies on our patients, not yet reported, tend to show that the blood volume is slightly below normal in schizophrenic as compared with that of control subjects. It can be assumed that the actual cell counts were relatively lower, therefore, than those reported, if allowance were made for concentration. This error, however, was presumably constant throughout the course of the studies. While we made no direct determinations of blood volumes in the particular group under thyroid treatment no systematic changes of concentration were noted in the chemical constituents of the blood. Kunde has shown by direct experiments in rabbits that the blood volume remained within normal limits following thyroid treatment in dosages that markely influenced the red cell counts. In therapeutic tests on human subjects, Blumgart, Gargill and Gilligan (16) have shown that in myxedemic patients, at least, thyroid medication tended to increase the plasma volume. If the same tendency exists in non-myxedemic subjects such as ours, the effect of the dilution would be to reduce the cell counts. Therefore, the erythropoietic effect we observed would gain in significance.

SUMMARY

Observations are reported on the effects of thyroid medication in varying dosages and for varying period of time on the blood pictures of 82 adult male schizophrenic patients.

The group averaged 30 years of age and had been in hospital for varying periods, averaging 3.3 years. As a group they were 16 per cent underweight and had "basal" metabolic rates 16 per cent below prediction. Some of the subjects were diagnosed initially as suffering from thyroid or other endocrine deficiencies whereas others were apparently not significantly abnormal in this regard.

The initial red cell counts averaged slightly below "normal" and the leukocyte counts slightly above. Other cell counts were essentially normal.

The average red cell counts of the entire group were significantly increased and the leukocyte counts slightly decreased following thyroid medication. In case of the leukocytes this effect was predominantly upon the polymorphonuclear cells, whereas the lymphocytes were relatively increased. Other white cells were not significantly affected.

In case of 52 patients initially anemic the red cell counts at first increased then decreased as the dosage was raised. There is, therefore, a median optimal dosage for this substance.

A similar diphasic effect on the white cells was noted.

The beneficial effect of a given dosage decreased with age.

A more pronounced effect was obtained in patients in normal nutrition than in underweight or overweight subjects.

The erythropoietic effect was in slight inverse ratio to the initial oxygen consumption rate.

The results are interpreted as being non-specific. They indicate that thyroid medication is of general utility for the treatment of secondary anemia and that age, nutritional status and basal metabolic rate, as well as dosage and duration of treatment, are significant factors in determining the degree of effect obtained.

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THE NERVOUS MANIFESTATIONS OF EXOPHTHALMIC GOITER AT DIFFERENT STAGES IN THE DISEASE*

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The peculiar nervous manifestations of Graves' disease have long fascinated those interested in the subject of goiter. It was in order to explain them that Plummer (1) (2) was led to postulate a dysthyroidism as well as a pure hyperthyroidism. According to this author, the thyroid gland of Graves' disease elaborates at least two products. One is abnormal, presumably deficiently iodinized thyroxine, and accounts for the peculiar nervous manifestations of the disease which distinguish it from toxic adenoma: the other is the normal hormone which is secreted in excess and accounts for a part or all of the increase in basal metabolism.

A careful clinical study of patients who have been followed for years after they had been restored to their usual state of health by thyroidectomy, suggests that the peculiar nervous manifestations of the disease may be accounted for in a simpler manner. From this study it would appear that most patients who develop exophthalmic goiter are naturally nervous, worrying, emotionally unstable individuals; that when they develop the disease all reactions that occur are merely exaggerations of reactions that previously were present in less intense form; and that when thyroidectomy restores the basal metabolic rate to normal, the patients themselves are merely restored to their former state of emotional instability.†

Careful questioning of a large number of patients over a long period has indicated that most of them were of the same general type before they developed exophthalmic goiter as after the disease had apparently disappeared. Moreover, careful observation of the same patients has shown that all reactions which were present when they were thyrotoxic usually persist in subdued form when they recover. If they talk very fast when thyrotoxic, they usually talk slightly fast when well. If emotional instability is outstanding when they are thyrotoxic, it is usually obvious when they are well. Thus, for example, if they weep particularly

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†According to Rautmann, Biedl and Redisch, Warthin, and Simpson, there is an actual physical basis for exophthalmic goiter, viz., an infantile or thymico-lymphatic constitution. (Rautmann, H.: Pathologisch-anatomische Untersuchungen über die Basedowsche Krankheit, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **28**: 489, 1915. Biedl, A. und Redisch, W.: Die Jodbehandlung der Hyperthyreosen, Med. Klin. **21**: 1371; 1413, 1925. Warthin, A. S.: The constitutional entity of exophthalmic goiter and so-called toxic adenoma, Ann. Int. Med. **2**: 553. 1928. Simpson, W. M.: Graves' constitution (Warthin): Am. J. Surg. **7**: 22. 1929. However, it should be stated that hypertrophy of the lymphatic system is not an invariable accompaniment of exophthalmic goiter.

easily when thyrotoxic, they usually burst into tears more easiy than the average person when well. If they move about particularly nervously when thyrotoxic, they usually find it difficult to sit very still when well. If their skin is particularly flushed when they are thyrotoxic, a slight flush persists when they get well. The fear, suspicion and marked tendency to worry about trifles that are so characteristic of exophthalmic goiter persist in milder form following recovery. This persistence of all thyrotoxic reactions in subdued form is true even of those patients who develop myxedema. These characteristics are usually present before the development of the thyrotoxicosis. It is not uncommon for the husbands of exophthalmic goiter patients to state that their wives were known as "Calamity Janes" before they developed the disease.

While a certain type of patient seems particularly susceptible to exophthalmic goiter it does not appear to be confined to this type. Apparently the most resistant can get it if the cause is acting with sufficient intensity. In other words, susceptibility is merely relative. This may explain why fairly calm and apparently stable individuals sometimes get the disease. In such patients the peculiar nervous manifestations are much less marked, often to the point where the diagnosis is doubted or the patients are thought to have toxic adenoma. When they recover, they do not manifest the emotional instability of other patients.

There is, of course, much discussion at the present time as to whether exophthalmic goiter and toxic adenoma are really different diseases and the question is still unanswered. It is of some interest, however, that patients who prove at operation and by pathological examination of the thyroid, to have so-called "toxic adenoma" are sometimes considered to have exophthalmic goiter before operation, because they have the nervous manifestations that usually accompany the latter. Exophthalmos is also occasionally seen in such cases (3) (4), although some observers claim that it does not occur in patient showing no hyperplastic changes in the gland surrounding the adenomatous tissue. Attempts to distinguish the two diseases on the basis of nervous manifestations alone not infrequently results in mistakes.

Thus, from an accurate knowledge of the personality of the patient before the disease developed, it should be possible to predict the type of reaction that would occur during the thyrotoxic period. It should also be possible, from a careful study of patients during the thyrotoxic period, to predict what they will be like following recovery. If this hypothesis be correct, it would be expected that certain persons who have never had exophthalmic goiter would resemble those who have suffered from the disease and have been "cured." Such cases have been described by various authors, (5) (6) (7) (8) (9) (10) (11) (12) (13) (14) (15), and are constantly being seen by men who do much goiter work. Indeed, they sometimes actually appear to have the disease. It is of interest that many soldiers who suffered from neurocirculatory asthenia during the war were

thought to have thyrotoxicosis before basal metabolism determinations were extensively carried out.

The fact that many patients do not appear quite normal even when their basal metabolism has been at a standard normal level for years after thyroidectomy has been used as an argument that the disease persists—possibly in the remnant of the thyroid gland. If the diagnosis of thyrotoxicosis following subtotal thyroidectomy were based on symptoms and not also on persistent elevation of the basal metabolism, its incidence would be very high. However, careful questioning will usually reveal that the patients are like they were years before the disease developed, and may, in fact, usually be regarded as cured if the basal metabolism is normal. Hyman and Kessel (6) expressed a similar idea when they stated that all that is to be expected of operation is to restore the patients to emotional instability. Moschowitz (5) put it very well when he remarked, "That which never disappears is the personality of the patient. The patient is still sensitive, emotional, restless, temperamental, sanguine, etc. Indeed, in this sense, the patient with Graves' disease is never completely cured, although he may be socially and economically restored." For this reason, several authors have claimed with some justification, that exophthalmic goiter is as much a disease of the sympathetic nervous system as it is of the thyroid gland (5) (6) (16).

Our hypothesis appears to be supported by observations which have been made on patients at different stages in their response to iodine (17) (18). It is Plummer's contention that, as long as iodine is given in excess, the peculiar characteristics of exphthalmic goiter are absent regardless of what happens to the basal metabolism (2). In other words, all the thyroid over-activity that is present is of the hyperthyroid form. Our observations have led to the conclusion that as long as the basal metabolic rate remains elevated when iodine is being given, all the signs and symptoms that were present before it was administered are still present in subdued form, and are more marked than following restoration of the basal metabolism to normal. That is, in each patient the intensity of the signs and symptoms roughly parallels the elevation of the basal metabolic rate. If, while iodine is being given, the basal metabolism rises higher than before its administration was started, all the peculiar nervous manifestations of exophthalmic goiter are likewise more marked than before it was started, regardless of the dose of iodine used. Thompson and Thompson have reported (17) two patients in whom exophthalmos first appeared and two in whom it became more marked as the basal metabolism was rising during the continuous administration of iodine. A patient has recently been observed in this clinic in whom exophthalmos first appeared during the administration of iodine following a hemithyroidectomy. It is of interest that the exophthalmos may appear before any of the other signs of the disease (4) (19) (20) and that it may first appear or may increase after the basal metabolism is restored to normal by a subtotal thyroidectomy (21) (22).

It has been possible to observe some patients who, during the continuous administration of iodine, developed partial and complete refractoriness to it, and to observe others who were initially refractory to it (17). At the time they are refractory, such patients differ in no other apparent respect from those who will respond well to iodine, except that the peculiar nervous manifestations of the disease are usually well marked. These observations are supported by the fact that operation during a period when the metabolism is rising rapidly in spite of the administration of large doses of iodine may be followed by a typical crisis and the death of the patient. As pointed out elsewhere (17), these crises are characterized by high fever, rapid pulse, profuse sweating, marked restlessness, nausea, vomiting and delirium, and are indistinguishable from those that occurred before the days of iodine. Similar reactions are sometimes seen following operation in patients who show an apparently satisfactory response to iodine. Pre-operative and post-operative administration of iodine do not completely abolish the post-operative reaction, although they reduce its incidence and intensity to a marked degree.

There appears to be no doubt about the truth of part of Plummer's hypothesis, viz., that the emotional reactions of patients with exophthalmic goiter are distinctive. The difference is merely in the explanation of this peculiarity. Plummer explains it on the basis of abnormal thyroxine, and we explain it as an exaggeration of an underlying emotional instability. We do not say that an abnormal thyroxine is not produced in exophthalmic goiter. We merely say that it seems unnecessary to postulate an abnormal hormone to account for the peculiar nervous manifestations of the disease. However, the evidence so far is against the production of a deficiently iodinized thyroxine. Thus, Gaddum (23), using material supplied by Harington, has recently shown that desiodothyroxine and diiodothyronine have little or no effect on the oxygen consumption of normal rats.

SUMMARY

In many quarters there has been a tendency to attribute the peculiar nervous manifestations of exophthalmic goiter to an abnormal thyroxine. Examination of a large number of patients over a long period of time has suggested that the nervous manifestations of the disease which may be grouped under the general heading of emotional instability, may be accounted for in a simpler manner. Briefly, it would appear that most patients who develop exophthalmic goiter were emotionally unstable before the development of the disease; that when the disease develops, all reactions that occur are merely exaggerations of reactions that previously were present in less intense form; and that when thyroidectomy restores the basal metabolic rate to normal, the patients themselves are merely restored to their former state of emotional instability. However, fairly calm and apparently stable individuals sometimes get the disease, possibly because the cause is acting with great intensity and susceptibility

is merely relative. In such patients the peculiar nervous manifestations are much less marked, often to the point where the diagnosis is doubted or the patients are thought to have toxic adenoma. When they recover they do not manifest the emotional instability of other patients. In other words, it would appear that the degree of emotional instability that is present in the disease depends largely upon the degree of emotional instability that was present before its development. No attempt is made to state what the precise pathological changes in exophthalmic goiter are.

CONCLUSION

The peculiar nervous manifestations of exophthalmic goiter appear to be satisfactorily explained as exaggerations of the customary reactions of the patients, who are usually of the emotionally unstable type.

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OPTIMAL WEIGHT ESTIMATION*

THE METHOD OF WILLOUGHBY

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The purpose of this paper is threefold: (1) to introduce the theory of the Willoughby method of anthropometry; (2) to demonstrate the technic of measuring and the computation of optimal weight therefrom; (3) after two years of use to discuss its clinical possibilities.

Mr. David P. Willoughby, medical artist and anthropometrist is, so far as I know, the sole originator of this thesis. Without benefit of training in the medical sciences, he has, through constant study, familiarized himself with the bony framework and musculature of the body far more than the average physician. There is perhaps no method of anthropometry with which he is not thoroughly familiar. The method to be presented is the culmination of many years' labor, during which period an appreciable number of physically excellent male and female individuals were used as experimental subjects. The principals propounded have been endorsed as basically sound by many capable observers (1). Whether or not his procedure supplants the older methods of weight computation, the work attests to a high degree of scientific endeavor.

The Willoughby method is applicable to all adult persons of the white race, irrespective of nationality or of so-called type or body build. It is based upon the principle that the fleshy parts of the body should be of a bulk in direct ratio to the size or thickness of the bony framework, irrespective of the height at which this is encountered. It, therefore, prescribes, the optimal, not the average, girth and diameter measurements, skeletal and fleshy, of every part of the body and, when considered with the height, it proposes a body-weight commensurate with these figures. That Mr. Willoughby is more interested in the optimal body-build than in the computation of body-weight therefrom, is borne out in his statement, "The possibility that an individual may be of the optimal weight prescribed for his height and bony framework, does not insure that he is properly proportioned. And since it is incontestable that the proportions of the body are of far greater physiologic significance than is the mere measure of his total bulk, it follows that the distribution of the fleshy tissues is the factor of most importance in connection with optimal body-build."

However true this may be, I have never found body disproportion of any great practical value in the elucidation of disease. Neither, as a clinician, am I interested in the artistic side of this theory. To a better method for the computation of optimal weight, however, one should lend one's attention. Long experience has taught us that there is some rela-

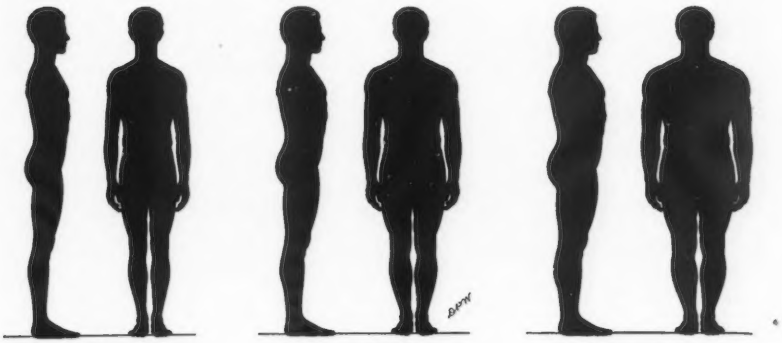
*Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions. New Orleans, May 9, 1932.

tionship between the skeletal framework of the individual and his weight. It has become a custom, when comparing persons of approximately the same height, to casually explain their weight differences by the variation in the size of their bones. We have perhaps looked upon this as merely a difference in the weight of the skeleton. Since the difference in weight between small-boned skeletons and large-bond skeletons, of approximately the same height, is actually only a few pounds, the soft tissues including the body fluids must make up for the greater weight variation in living subjects. It stands to reason that a large-boned person should of necessity have larger muscles than a small-boned person. He should also possess

OPTIMAL PROPORTIONS OF THE HUMAN FIGURE

IN APPLICATION TO DIFFERENT DEGREES OF SKELETAL THICKNESS

- Male Adult -



Skeleton 15 per cent Thinner than Medium

Skeleton of Medium Thickness in relation to Stature

Skeleton 15 per cent Thicker than Medium

©D.R.W.

a greater amount of interstitial tissue, a circulatory system commensurate to his bulk and sufficient fat padding and fluids to insure him not only health but physical harmony.

Of the various theories dealing with the weight controlling mechanism of the body, we are not concerned in this paper. Somewhere between the contentions of Newburgh (2), who doubts the existence of endogenous obesity, and those of Gigon (3), who denies the existence of exogenous obesity, the truth will ultimately be discovered. Perhaps the best discussion of this problem may be found in a recent article by Silver and Bauer (4). Whatever the etiology, we have learned that a marked variation from the normal body weight is not conducive to health and longevity. In the light of this knowledge, it becomes increasingly necessary to redefine the normal; better still, to get away from any standard erroneously based on the law of averages and attempt to procure something more ideal. Anything which will lend itself to a better understanding of this subject should be considered a distinct advance. In my opinion, the Willoughby method is a step in the right direction.

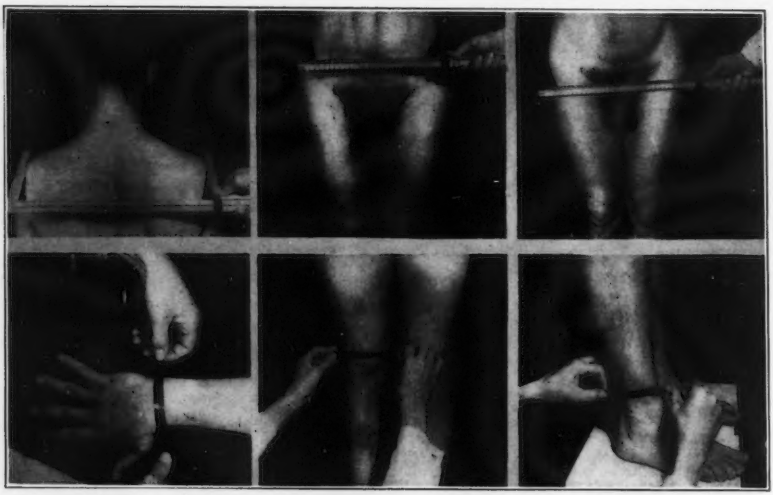


Figure 1. Showing method of measuring.

Method of Measuring: Six skeletal measurements are employed in this technic. Three of these are diameter measurements of the trunk and three are circumference measurements of the extremities, as follows:

The Diameter Measurements:

(1) Bisacromial
(2) Bi-iliac
(3) Bitrochanteric

The Circumference Measurements:

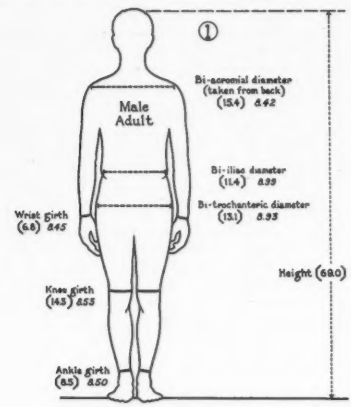
(1) Wrist
(2) Knee
(3) Ankle

The bisacromial diameter is secured (facing the back of the subject) by pressing the extremities of the calipers firmly against the most lateral projections of the acromion processes. The bi-iliac diameter is taken from in front, the points of the calipers being pressed firmly against the most lateral extensions of the iliac crests. The bitrochanteric diameter is taken from in front, the points of the calipers being applied as closely to the most lateral projections of the greater trochanters as is expedient. In taking each of these three diameter measurements, the bony points should first be definitely located by palpating with the finger tips.

The girth of wrist is measured between the styloid process and the hand, with the hand open, the fingers extended, and the hand in line with the forearm. The girth of knee is taken over the central level of the patella, with the thigh muscles relaxed, but knees straight and with the weight distributed equally on both feet. The girth of ankle is taken at

the smallest part, about two inches above the malleoli; as in the former measurement it is essential that the subject's weight be distributed equally on both feet.

EXAMPLE TO SHOW HOW THE OPTIMAL GIRTH MEASUREMENTS AND BODY WEIGHT TO APPLY TO THE OBSERVED MEASUREMENTS IN HEIGHT AND SKELETAL THICKNESS, ARE ARRIVED AT:-



Measurements in brackets, ( ), indicate *observed* measurements of skeleton.

Measurements in italics, *8.42* etc., indicate *implied* sizes of ankle girth to correspond with respective observed measurements.

②

Mean of six values of ankle girth, or "Corrected Ankle Girth" =

8.42 × 1, or 8.42
8.45 × 2, or 16.90
8.50 × 3, or 25.50
8.53 × 3, or 25.59
8.93 × 2, or 17.86
8.99 × 1, or 8.99
12 | 103.26
or, 8.60+

OPTIMAL MEASUREMENTS IN RELATION TO SKELETAL THICKNESS

Extract (for 8.60 measurement) from Tabulation comprising *all* sizes of Corrected Ankle Girth:

Correct 1 Ankle Girth, inches	Skeletal Measurements, inches							Fleshy measurements, inches									Body Weight, pounds, per inch of height
	Diameters				Girths			Diam.	Girths								
	Bi-acromial	Chest (Trans.)	Chest (Ant.-post.)	Bi-iliac	Bi-trochanteric	Wrist	Knee	Ankle	Bi-deltoid	Neck	Upper Arm (Flexed)	Forearm	Chest (normal)	Waist	Hips	Thigh	Calf	
8.60	15.7	11.7	8.1	10.9	12.6	6.9	14.4	—	18.9	15.5	14.5	12.1	40.4	30.3	34.6	21.6	14.6	2.520 ⑤

③ ④→ ⑤ Therefore, body weight = 2.520 × 69.0, or 160 pounds.

Computation of Optimal Weight: While the theory and technical details of this procedure may be found in the original article by Willoughby (5), a brief explanation of the four major steps will be given here.

(1) By a series of mathematical calculations each of the six measurements is converted into a value representing the optimal ankle girth corresponding with that measurement.

(2) From these five implied values plus the actual ankle girth, a mean or weighted average termed the "corrected ankle girth" is derived.

(3) A factor representing body weight in pounds per inch of height has been worked out to correlate with the "corrected ankle girth" as found.

(4) The height in inches times this factor equals the optimal weight.

This process appears involved and at the beginning of our observation it was complicated, taking not only time but considerable ingenuity. At present, however, by the use of tables the whole computation may be made in less than five minutes.

Step 1, or the conversion of actual measurements into implied ankle girth, is carried out as shown by Table A (male and female).

Step 2, or the derivation of the "corrected ankle girth" (in reality but a weighted average of the aforementioned figures), takes longer since the calculation must be made in every case as shown.

TABLE FOR DERIVING PROPORTIONATE ANKLE GIRTH FROM OTHER SKELETAL DIMENSIONS

For use in the Willoughby System of Anthropometric Diagnosis.

MALE

BI-ACROMIAL DIAMETER : ANKLE GIRTH						BI-ILIAC DIAMETER : ANKLE GIRTH						BI-TROCHANTERIC DIAMETER : ANKLE GIRTH						WRIST GIRTH : ANKLE GIRTH				KNEE GIRTH : ANKLE GIRTH					
13.5	7.39	15.2	8.32	16.9	9.25	9.35	7.37	10.55	8.32	11.75	9.27	10.85	7.40	12.2	8.32	13.55	9.24	5.95	7.39	7.1	8.82	12.4	7.40	13.95	8.32	15.5	9.25
13.55	7.41	15.25	8.34	16.95	9.27																	12.45	7.43	14.0	8.35	15.55	9.28
13.6	7.44	15.3	8.37	17.0	9.30	9.4	7.41	10.6	8.36	11.8	9.31	10.9	7.43	12.25	8.35	13.6	9.27	6.0	7.45	7.15	8.88	12.5	7.46	14.05	8.38	15.6	9.31
13.65	7.47	15.35	8.40	17.05	9.33	9.45	7.45	10.65	8.40	11.85	9.35	10.95	7.46	12.3	8.38	13.65	9.30					12.55	7.49	14.1	8.41	15.65	9.34
13.7	7.49	15.4	8.42	17.1	9.35							11.0	7.50	12.35	8.41	13.7	9.34	6.05	7.52	7.2	8.95						
13.75	7.52	15.45	8.45	17.15	9.38	9.5	7.49	10.7	8.44	11.9	9.38											12.6	7.52	14.15	8.44	15.7	9.37
13.8	7.55	15.5	8.48	17.2	9.41							11.05	7.53	12.4	8.45	13.75	9.37	6.1	7.58	7.25	9.01	12.65	7.55	14.2	8.47	15.75	9.40
13.85	7.57	15.55	8.51	17.25	9.44	9.55	7.53	10.75	8.48	11.95	9.42											12.7	7.58	14.25	8.50	15.8	9.43
13.9	7.60	15.6	8.53	17.3	9.46							11.1	7.57	12.45	8.49	13.8	9.41	6.15	7.64	7.3	9.07						
13.95	7.63	15.65	8.56	17.35	9.49	9.6	7.57	10.8	8.52	12.0	9.46											12.75	7.61	14.3	8.53	15.85	9.46
14.0	7.66	15.7	8.59	17.4	9.52							11.15	7.60	12.5	8.52	13.85	9.44	6.2	7.70	7.35	9.13						
14.05	7.69	15.75	8.62	17.45	9.55	9.65	7.61	10.85	8.56	12.05	9.50											12.8	7.64	14.35	8.56	15.9	9.49
14.1	7.71	15.8	8.64	17.5	9.57							11.2	7.63	12.55	8.55	13.9	9.48	6.25	7.76	7.4	9.19						
14.15	7.74	15.85	8.67	17.55	9.60	9.7	7.65	10.9	8.60	12.1	9.54											12.85	7.67	14.4	8.59	15.95	9.52
14.2	7.77	15.9	8.70	17.6	9.63							11.25	7.67	12.6	8.59	13.95	9.51	6.3	7.83	7.45	9.25	12.9	7.70	14.45	8.62	16.0	9.55
14.25	7.80	15.95	8.73	17.65	9.66	9.75	7.69	10.95	8.64	12.15	9.58											12.95	7.73	14.5	8.65	16.05	9.58
14.3	7.82	16.0	8.75	17.7	9.68							11.3	7.70	12.65	8.62	14.0	9.54										
14.35	7.85	16.05	8.78	17.75	9.71	9.8	7.73	11.0	8.68	12.2	9.62	11.35	7.74	12.7	8.66	14.05	9.58	6.35	7.89	7.5	9.32	13.0	7.76	14.55	8.68	16.1	9.61
14.4	7.88	16.1	8.81	17.8	9.74																	13.05	7.79	14.6	8.71	16.15	9.64
14.45	7.90	16.15	8.83	17.85	9.76	9.85	7.77	11.05	8.71	12.25	9.66	11.4	7.77	12.75	8.69	14.1	9.61	6.4	7.95	7.55	9.38	13.1	7.82	14.65	8.74	16.2	9.67
14.5	7.93	16.2	8.86	17.9	9.79							11.45	7.80	12.8	8.73	14.15	9.64										
14.55	7.96	16.25	8.89	17.95	9.82	9.9	7.81	11.1	8.75	12.3	9.70							6.45	8.01	7.6	9.44	13.15	7.85	14.7	8.77	16.25	9.70
14.6	7.99	16.3	8.92	18.0	9.85							11.5	7.84	12.85	8.76	14.2	9.68	6.5	8.07	7.65	9.50						
14.65	8.01	16.35	8.94	18.05	9.87	9.95	7.85	11.15	8.79	12.35	9.74											13.2	7.88	14.75	8.80	16.3	9.73
14.7	8.04	16.4	8.97	18.1	9.90							11.55	7.87	12.9	8.79	14.25	9.71	6.55	8.14	7.7	9.57	13.25	7.91	14.8	8.83	16.35	9.76
14.75	8.07	16.45	9.00	18.15	9.93	10.0	7.89	11.2	8.83	12.4	9.78																
14.8	8.10	16.5	9.03	18.2	9.96							11.6	7.91	12.95	8.82	14.3	9.75	6.6	8.20	7.75	9.63	13.3	7.94	14.85	8.86	16.4	9.79
14.85	8.12	16.55	9.05	18.25	9.98	10.05	7.93	11.25	8.87	12.45	9.82																
14.9	8.15	16.6	9.08	18.3	10.01							11.65	7.94	13.0	8.86	14.35	9.78	6.65	8.26	7.8	9.69	13.35	7.97	14.9	8.89	16.45	9.82
14.95	8.18	16.65	9.11	18.35	10.04	10.1	7.97	11.3	8.91	12.5	9.86																
15.0	8.21	16.7	9.14	18.4	10.07							11.7	7.98	13.05	8.90	14.4	9.82	6.7	8.32	7.85	9.75	13.4	8.00	14.95	8.92	16.5	9.84
15.05	8.23	16.75	9.16	18.45	10.09	10.15	8.00	11.35	8.95	12.55	9.90																
15.1	8.26	16.8	9.19	18.5	10.12							11.75	8.01	13.1	8.93	14.45	9.85	6.75	8.39	7.9	9.81	13.45	8.02	15.0	8.95	16.55	9.87
15.15	8.29	16.85	9.22	18.55	10.15	10.2	8.04	11.4	8.99	12.6	9.94	11.8	8.04	13.15	8.96	14.5	9.88					13.5	8.05	15.05	8.98	16.6	9.90
												11.85	8.08	13.2	9.00	14.55	9.92	6.8	8.45	7.95	9.88	13.55	8.08	15.1	9.01	16.65	9.93
						10.25	8.08	11.45	9.03	12.65	9.98																
												11.9	8.11	13.25	9.03	14.6	9.95	6.85	8.51	8.0	9.94	13.6	8.11	15.15	9.04	16.7	9.96
						10.3	8.12	11.5	9.07	12.7	10.02																
												11.95	8.14	13.3	9.07	14.65	9.99	6.9	8.57	8.05	10.00	13.65	8.14	15.2	9.07	16.75	9.99
						10.35	8.16	11.55	9.11	12.75	10.06																
												12.0	8.18	13.35	9.10	14.7	10.02	6.95	8.63	8.1	10.06	13.7	8.17	15.25	9.10	16.8	10.02
						10.4	8.20	11.6	9.15	12.8	10.09																
												12.05	8.21	13.4	9.13	14.75	10.05	7.0	8.70	8.15	10.12	13.75	8.20	15.3	9.13	16.85	10.03
						10.45	8.24	11.65	9.19	12.85	10.13																
												12.1	8.25	13.45	9.17	14.8	10.09					13.8	8.23	15.35	9.16	16.9	10.08
						10.5	8.28	11.7	9.23	12.9	10.17																
												12.15	8.28	13.5	9.20	14.85	10.12	7.05	8.76	8.2	10.19	13.85	8.26	15.4	9.19	16.95	10.11
																						13.9	8.29	15.45	9.22	17.0	10.14

Table A (Male). Showing how actual measurements are converted into implied or theoretical ankle girths. The converted figure appears to the right of the actual measurement.

FEMALE

BI-ACROMIAL DIAMETER : ANKLE GIRTH					
11.8	6.98	13.15	7.78	14.5	8.57
11.85	7.01	13.2	7.81	14.55	8.60
11.9	7.04	13.25	7.84	14.6	8.63
11.95	7.07	13.3	7.87	14.65	8.66
12.0	7.10	13.35	7.89	14.7	8.69
12.05	7.13	13.4	7.92	14.75	8.72
12.1	7.16	13.45	7.95	14.8	8.75
12.15	7.19	13.5	7.98	14.85	8.78
12.2	7.21	13.55	8.01	14.9	8.81
12.25	7.24	13.6	8.04	14.95	8.84
12.3	7.27	13.65	8.07	15.0	8.87
12.35	7.30	13.7	8.10	15.05	8.90
12.4	7.33	13.75	8.13	15.1	8.93
12.45	7.36	13.8	8.16	15.15	8.96
12.5	7.39	13.85	8.19	15.2	8.99
12.55	7.42	13.9	8.22	15.25	9.02
12.6	7.45	13.95	8.25	15.3	9.05
12.65	7.48	14.0	8.28	15.35	9.08
12.7	7.51	14.05	8.31	15.4	9.11
12.75	7.54	14.1	8.34	15.45	9.14
12.8	7.57	14.15	8.37	15.5	9.17
12.85	7.60	14.2	8.40	15.55	9.20
12.9	7.63	14.25	8.43	15.6	9.23
12.95	7.66	14.3	8.46	15.65	9.25
13.0	7.69	14.35	8.49	15.7	9.28
13.05	7.72	14.4	8.52	15.75	9.31
13.1	7.75	14.45	8.55	15.8	9.34

BI-ILIAC DIAMETER : ANKLE GIRTH					
9.35	6.97	10.45	7.79	11.55	8.61
9.4	7.01	10.5	7.83	11.6	8.65
9.45	7.05	10.55	7.87	11.65	8.69
9.5	7.08	10.6	7.90	11.7	8.72
9.55	7.12	10.65	7.94	11.75	8.76
9.6	7.16	10.7	7.98	11.8	8.80
9.65	7.20	10.75	8.02	11.85	8.84
9.7	7.23	10.8	8.05	11.9	8.87
9.75	7.27	10.85	8.09	11.95	8.91
9.8	7.31	10.9	8.13	12.0	8.95
9.85	7.35	10.95	8.17	12.05	8.99
9.9	7.38	11.0	8.20	12.1	9.02
9.95	7.42	11.05	8.24	12.15	9.06
10.0	7.46	11.1	8.28	12.2	9.10
10.05	7.49	11.15	8.31	12.25	9.13
10.1	7.53	11.2	8.35	12.3	9.17
10.15	7.57	11.25	8.39	12.35	9.21
10.2	7.61	11.3	8.43	12.4	9.25
10.25	7.64	11.35	8.46	12.45	9.28
10.3	7.68	11.4	8.50	12.5	9.32
10.35	7.72	11.45	8.54	12.55	9.36
10.4	7.76	11.5	8.57	12.6	9.40

BI-TROCHANTERIC DIAMETER : ANKLE GIRTH					
10.55	6.98	11.75	7.76	12.95	8.57
10.6	7.02	11.8	7.81	13.0	8.60
10.65	7.05	11.85	7.84	13.05	8.64
10.7	7.08	11.9	7.88	13.1	8.67
10.75	7.11	11.95	7.91	13.15	8.70
10.8	7.14	12.0	7.94	13.2	8.74
10.85	7.18	12.05	7.97	13.25	8.77
10.9	7.21	12.1	8.01	13.3	8.80
10.95	7.25	12.15	8.04	13.35	8.84
11.0	7.28	12.2	8.07	13.4	8.87
11.05	7.31	12.25	8.11	13.45	8.90
11.1	7.34	12.3	8.14	13.5	8.93
11.15	7.38	12.35	8.17	13.55	8.97
11.2	7.41	12.4	8.21	13.6	9.00
11.25	7.45	12.45	8.24	13.65	9.03
11.3	7.48	12.5	8.27	13.7	9.07
11.35	7.51	12.55	8.31	13.75	9.10
11.4	7.54	12.6	8.34	13.8	9.13
11.45	7.58	12.65	8.37	13.85	9.17
11.5	7.61	12.7	8.41	13.9	9.20
11.55	7.64	12.75	8.44	13.95	9.23
11.6	7.68	12.8	8.47	14.0	9.27
11.65	7.71	12.85	8.50	14.05	9.30
11.7	7.74	12.9	8.54	14.1	9.33

WRIST GIRTH : ANKLE GIRTH			
5.15	6.96	6.05	8.17
5.2	7.02	6.1	8.24
5.25	7.09	6.15	8.31
5.3	7.16	6.2	8.37
5.35	7.23	6.25	8.44
5.4	7.29	6.3	8.51
5.45	7.36	6.35	8.58
5.5	7.43	6.4	8.65
5.55	7.50	6.45	8.71
5.6	7.56	6.5	8.78
5.65	7.63	6.55	8.85
5.7	7.70	6.6	8.92
5.75	7.77	6.65	8.98
5.8	7.83	6.7	9.05
5.85	7.90	6.75	9.12
5.9	7.97	6.8	9.19
5.95	8.04	6.85	9.25
6.0	8.10	6.9	9.32

KNEE GIRTH : ANKLE GIRTH					
11.85	6.99	13.2	7.79	14.55	8.58
11.9	7.02	13.25	7.82	14.6	8.61
11.95	7.05	13.3	7.85	14.65	8.64
12.0	7.08	13.35	7.88	14.7	8.67
12.05	7.11	13.4	7.91	14.75	8.70
12.1	7.14	13.45	7.94	14.8	8.73
12.15	7.17	13.5	7.96	14.85	8.76
12.2	7.20	13.55	7.99	14.9	8.79
12.25	7.23	13.6	8.02	14.95	8.82
12.3	7.26	13.65	8.05	15.0	8.85
12.35	7.29	13.7	8.08	15.05	8.88
12.4	7.32	13.75	8.11	15.1	8.91
12.45	7.35	13.8	8.14	15.15	8.94
12.5	7.37	13.85	8.17	15.2	8.97
12.55	7.40	13.9	8.20	15.25	9.00
12.6	7.43	13.95	8.23	15.3	9.03
12.65	7.46	14.0	8.26	15.35	9.06
12.7	7.49	14.05	8.29	15.4	9.09
12.75	7.52	14.1	8.32	15.45	9.12
12.8	7.55	14.15	8.35	15.5	9.14
12.85	7.58	14.2	8.38	15.55	9.17
12.9	7.61	14.25	8.41	15.6	9.20
12.95	7.64	14.3	8.44	15.65	9.23
13.0	7.67	14.35	8.47	15.7	9.26
13.05	7.70	14.4	8.50	15.75	9.29
13.1	7.73	14.45	8.53	15.8	9.32
13.15	7.76	14.5	8.55	15.85	9.35

DPW 10-31

Table A (Female).

OPTIMUM PROPORTIONS of the BODY in relation to "CORRECTED" ANKLE GIRTH

MALE (Adult)

Corrected Ankle Girth, inches	Skeletal measurements, inches										Fleshy measurements, inches												Body weight, Pounds, per inch of height
	Diameters					Girths					Diam.	Girths											
	Bi-acromial	Chest Trans.	Chest Ant.-post.	Bi-iliac	Bi-trochanteric	Wrist R.	Wrist L.	Knee R.	Knee L.	Ankle R.	Ankle L.	Bi-deltoid	Neck	Upper arm, flexed R.	Upper arm, flexed L.	Forearm R.	Forearm L.	Chest normal	Waist	Hips	Thigh R.	Thigh L.	Calf R.	Calf L.	
7.4	13.5	10.0	7.0	9.4	10.9	6.0	6.0	12.4	12.4	—	—	16.3	13.3	12.4	12.4	10.4	10.4	34.7	26.1	31.5	18.8	18.8	12.5	12.5	1.720
7.45	13.6	10.1	7.0	9.4	10.9	6.0	6.0	12.5	12.5	—	—	16.4	13.4	12.5	12.5	10.5	10.5	35.0	26.2	31.7	18.9	18.9	12.6	12.6	1.743
7.5	13.7	10.2	7.0	9.5	11.0	6.0	6.0	12.6	12.6	—	—	16.5	13.5	12.6	12.6	10.5	10.5	35.2	26.4	31.9	19.0	19.0	12.7	12.7	1.766
7.55	13.8	10.2	7.1	9.6	11.1	6.1	6.1	12.7	12.7	—	—	16.6	13.6	12.7	12.7	10.6	10.6	35.4	26.6	32.2	19.2	19.2	12.8	12.8	1.789
7.6	13.9	10.3	7.1	9.6	11.1	6.1	6.1	12.7	12.7	—	—	16.7	13.7	12.8	12.8	10.7	10.7	35.7	26.8	32.4	19.3	19.3	12.9	12.9	1.812
7.65	14.0	10.4	7.2	9.7	11.2	6.2	6.2	12.8	12.8	—	—	16.8	13.8	12.9	12.9	10.7	10.7	35.9	26.9	32.6	19.4	19.4	13.0	13.0	1.836
7.7	14.1	10.4	7.2	9.8	11.3	6.2	6.2	12.9	12.9	—	—	16.9	13.9	12.9	12.9	10.8	10.8	36.2	27.1	32.8	19.6	19.6	13.0	13.0	1.860
7.75	14.2	10.5	7.3	9.8	11.4	6.2	6.2	13.0	13.0	—	—	17.0	14.0	13.0	13.0	10.9	10.9	36.4	27.3	33.0	19.7	19.7	13.1	13.1	1.884
7.8	14.3	10.6	7.3	9.9	11.4	6.3	6.3	13.1	13.1	—	—	17.2	14.1	13.1	13.1	11.0	11.0	36.6	27.5	33.2	19.8	19.8	13.2	13.2	1.908
7.85	14.3	10.7	7.4	10.0	11.5	6.3	6.3	13.2	13.2	—	—	17.3	14.1	13.2	13.2	11.0	11.0	36.9	27.6	33.4	19.9	19.9	13.3	13.3	1.933
7.9	14.4	10.7	7.4	10.0	11.6	6.4	6.4	13.2	13.2	—	—	17.4	14.2	13.3	13.3	11.1	11.1	37.1	27.8	33.7	20.1	20.1	13.4	13.4	1.958
7.95	14.5	10.8	7.5	10.1	11.7	6.4	6.4	13.3	13.3	—	—	17.5	14.3	13.4	13.4	11.2	11.2	37.3	28.0	33.9	20.2	20.2	13.5	13.5	1.983
8.0	14.6	10.9	7.5	10.1	11.7	6.4	6.4	13.4	13.4	—	—	17.6	14.4	13.4	13.4	11.2	11.2	37.6	28.2	34.1	20.3	20.3	13.5	13.5	2.008
8.05	14.7	10.9	7.6	10.2	11.8	6.5	6.5	13.5	13.5	—	—	17.7	14.5	13.5	13.5	11.3	11.3	37.8	28.4	34.3	20.4	20.4	13.6	13.6	2.033
8.1	14.8	11.0	7.6	10.3	11.9	6.5	6.5	13.6	13.6	—	—	17.8	14.6	13.6	13.6	11.4	11.4	38.0	28.5	34.5	20.6	20.6	13.7	13.7	2.058
8.15	14.9	11.1	7.7	10.3	12.0	6.6	6.6	13.7	13.7	—	—	17.9	14.7	13.7	13.7	11.5	11.5	38.3	28.7	34.7	20.7	20.7	13.8	13.8	2.084
8.2	15.0	11.1	7.7	10.4	12.0	6.6	6.6	13.7	13.7	—	—	18.0	14.8	13.8	13.8	11.5	11.5	38.5	28.9	34.9	20.8	20.8	13.9	13.9	2.109
8.25	15.1	11.2	7.8	10.5	12.1	6.6	6.6	13.8	13.8	—	—	18.1	14.9	13.9	13.9	11.6	11.6	38.7	29.1	35.2	20.9	20.9	14.0	14.0	2.135
8.3	15.2	11.3	7.8	10.5	12.2	6.7	6.7	13.9	13.9	—	—	18.3	15.0	14.0	14.0	11.7	11.7	39.0	29.2	35.4	21.1	21.1	14.1	14.1	2.161
8.35	15.3	11.3	7.8	10.6	12.2	6.7	6.7	14.0	14.0	—	—	18.4	15.0	14.0	14.0	11.7	11.7	39.2	29.4	35.6	21.2	21.2	14.1	14.1	2.187
8.4	15.3	11.4	7.9	10.7	12.3	6.8	6.8	14.1	14.1	—	—	18.5	15.1	14.1	14.1	11.8	11.8	39.4	29.6	35.8	21.3	21.3	14.2	14.2	2.213
8.45	15.4	11.5	7.9	10.7	12.4	6.8	6.8	14.2	14.2	—	—	18.6	15.2	14.2	14.2	11.9	11.9	39.7	29.8	36.0	21.5	21.5	14.3	14.3	2.239
8.5	15.5	11.5	8.0	10.8	12.5	6.8	6.8	14.2	14.2	—	—	18.7	15.3	14.3	14.3	11.9	11.9	39.9	29.9	36.2	21.6	21.6	14.4	14.4	2.266
8.55	15.6	11.6	8.0	10.8	12.5	6.9	6.9	14.3	14.3	—	—	18.8	15.4	14.4	14.4	12.0	12.0	40.1	30.1	36.4	21.7	21.7	14.5	14.5	2.293
8.6	15.7	11.7	8.1	10.9	12.6	6.9	6.9	14.4	14.4	—	—	18.9	15.5	14.5	14.5	12.1	12.1	40.4	30.3	36.6	21.8	21.8	14.6	14.6	2.320
8.65	15.8	11.7	8.1	11.0	12.7	7.0	7.0	14.5	14.5	—	—	19.0	15.6	14.5	14.5	12.2	12.2	40.6	30.5	36.9	22.0	22.0	14.6	14.6	2.347
8.7	15.9	11.8	8.2	11.0	12.8	7.0	7.0	14.6	14.6	—	—	19.1	15.7	14.6	14.6	12.2	12.2	40.8	30.6	37.1	22.1	22.1	14.7	14.7	2.374
8.75	16.0	11.9	8.2	11.1	12.8	7.0	7.0	14.7	14.7	—	—	19.2	15.8	14.7	14.7	12.3	12.3	41.1	30.8	37.3	22.2	22.2	14.8	14.8	2.401
8.8	16.1	12.0	8.3	11.2	12.9	7.1	7.1	14.7	14.7	—	—	19.4	15.9	14.8	14.8	12.4	12.4	41.3	31.0	37.5	22.3	22.3	14.9	14.9	2.429
8.85	16.2	12.0	8.3	11.2	13.0	7.1	7.1	14.8	14.8	—	—	19.5	15.9	14.9	14.9	12.4	12.4	41.6	31.2	37.7	22.5	22.5	15.0	15.0	2.457
8.9	16.3	12.1	8.4	11.3	13.1	7.2	7.2	14.9	14.9	—	—	19.6	16.0	15.0	15.0	12.5	12.5	41.8	31.3	37.9	22.6	22.6	15.1	15.1	2.485
8.95	16.3	12.2	8.4	11.4	13.1	7.2	7.2	15.0	15.0	—	—	19.7	16.1	15.0	15.0	12.6	12.6	42.0	31.5	38.1	22.7	22.7	15.1	15.1	2.513
9.0	16.4	12.2	8.5	11.4	13.2	7.2	7.2	15.1	15.1	—	—	19.8	16.2	15.1	15.1	12.6	12.6	42.3	31.7	38.3	22.9	22.9	15.2	15.2	2.541
9.05	16.5	12.3	8.5	11.5	13.3	7.3	7.3	15.2	15.2	—	—	19.9	16.3	15.2	15.2	12.7	12.7	42.5	31.9	38.6	23.0	23.0	15.3	15.3	2.569
9.1	16.6	12.4	8.6	11.5	13.3	7.3	7.3	15.3	15.3	—	—	20.0	16.4	15.3	15.3	12.8	12.8	42.7	32.0	38.8	23.1	23.1	15.4	15.4	2.597
9.15	16.7	12.4	8.6	11.6	13.4	7.4	7.4	15.3	15.3	—	—	20.1	16.5	15.4	15.4	12.9	12.9	43.0	32.2	39.0	23.2	23.2	15.5	15.5	2.626
9.2	16.8	12.5	8.6	11.7	13.5	7.4	7.4	15.4	15.4	—	—	20.2	16.6	15.5	15.5	12.9	12.9	43.2	32.4	39.2	23.4	23.4	15.6	15.6	2.655
9.25	16.9	12.6	8.7	11.7	13.6	7.4	7.4	15.5	15.5	—	—	20.3	16.7	15.5	15.5	13.0	13.0	43.4	32.6	39.4	23.5	23.5	15.7	15.7	2.684
9.3	17.0	12.6	8.7	11.8	13.6	7.5	7.5	15.6	15.6	—	—	20.5	16.8	15.6	15.6	13.1	13.1	43.7	32.8	39.6	23.6	23.6	15.7	15.7	2.713
9.35	17.1	12.7	8.8	11.9	13.7	7.5	7.5	15.7	15.7	—	—	20.6	16.8	15.7	15.7	13.1	13.1	43.9	32.9	39.8	23.7	23.7	15.8	15.8	2.742
9.4	17.2	12.8	8.8	11.9	13.8	7.6	7.6	15.8	15.8	—	—	20.7	16.9	15.8	15.8	13.2	13.2	44.1	33.1	40.0	23.9	23.9	15.9	15.9	2.772
9.45	17.3	12.8	8.9	12.0	13.9	7.6	7.6	15.8	15.8	—	—	20.8	17.0	15.9	15.9	13.3	13.3	44.4	33.3	40.3	24.0	24.0	16.0	16.0	2.801
9.5	17.4	12.9	8.9	12.0	13.9	7.6	7.6	15.9	15.9	—	—	20.9	17.1	16.0	16.0	13.3	13.3	44.6	33.5	40.5	24.1	24.1	16.1	16.1	2.831
9.55	17.4	13.0	9.0	12.1	14.0	7.7	7.7	16.0	16.0	—	—	21.0	17.2	16.1	16.1	13.4	13.4	44.8	33.6	40.7	24.2	24.2	16.2	16.2	2.861
9.6	17.5	13.0	9.0	12.2	14.1	7.7	7.7	16.1	16.1	—	—	21.1	17.5	16.1	16.1	13.5	13.5	45.1	33.8	40.9	24.4	24.4	16.3	16.3	2.891
9.65	17.6	13.1	9.1	12.2	14.2	7.8	7.8	16.2	16.2	—	—	21.2	17.6	16.2	16.2	13.6	13.6	45.3	34.0	41.1	24.5	24.5	16.3	16.3	2.921
9.7	17.7	13.2	9.1	12.3	14.2	7.8	7.8	16.3	16.3	—	—	21.3	17.5	16.3	16.3	13.6	13.6	45.5	34.2	41.3	24.6	24.6	16.4	16.4	2.951
9.75	17.8	13.2	9.2	12.4	14.3	7.8	7.8	16.3	16.3	—	—	21.4	17.6	16.4	16.4	13.7	13.7	45.8	34.3	41.5	24.8	24.8	16.5	16.5	2.981
9.8	17.9	13.3	9.2	12.4	14.4	7.9	7.9	16.4	16.4	—	—	21.6	17.7	16.5	16.5	13.8	13.8	46.0	34.5	41.7	24.9	24.9	16.6	16.6	3.012
9.85	18.0	13.4	9.3	12.5	14.4	7.9	7.9	16.5	16.5	—	—	21.7	17.7	16.6	16.6	13.8	13.8	46.2	34.7	42.0	25.0	25.0	16.7	16.7	3.043
9.9	18.1	13.4	9.3	12.5	14.5	8.0	8.0	16.6	16.6	—	—	21.8	17.8	16.6	16.6	13.9	13.9	46.5	34.9	42.2	25.1	25.1	16.8	16.8	3.074
9.95	18.2	13.5	9.4	12.6	14.6	8.0	8.0	16.7	16.7	—	—	21.9	17.9	16.7	16.7	14.0	14.0	46.7	35.1	42.4	25.3	25.3	16.8	16.8	3.105
10.0	18.3	13.6	9.4	12.7	14.7	8.0	8.0	16.8	16.8	—	—	22.0	18.0	16.8	16.8	14.0	14.0	46.9	35.2	42.6	25.4	25.4	16.9	16.9	3.136
10.05	18.4	13.6	9.4	12.7	14.7	8.1	8.1	16.9	16.8	—	—	22.1	18.1	16.9	16.9	14.1	14.1	47.2	35.4	42.8	25.5	25.5	17.0	17.0	3.167
10.1	18.5	13.7	9.5	12.8	14.8	8.1	8.1	16.9	16.9	—	—	22.2	18.2	17.0	17.0	14.2	14.2	47.4	35.6	43.0	25.6	25.6	17.1	17.1	3.199
10.15	18.5	13.8	9.5	12.9	14.9	8.2	8.2	17.0	17.0	—	—	22.3	18.3	17.1	17.1	14.3	14.3	47.7	35.7	43.3	25.8	25.8	17.2	17.2	3.231
10.2	18.6	13.9	9.6	12.9	15.0	8.2	8.2	17.1	17.1	—	—	22.4	18.4	17.1	17.1	14.3	14.3	47.9	35.9	43.5	25.9	25.9	17.3	17.3	3.263

Table B (Male). Factors are given in the last column at the right to correspond with "Corrected ankle girth" shown in first column on the left. This factor times the height in inches equals the optimal weight.

Step 3, or the finding of a factor representing body weight in pounds per inch of height to correlate with this figure, is again made easy by Table B (male and female).

Step 4 is the multiplication of this factor by the height in inches, which results in the optimal weight.

In order to determine the degree of technical accuracy, the following test was made. Five subjects were measured by five examiners and their optimal wights computated independently. Examiners 1, 2 and 3 were

FEMALE (Adult)

Corrected Ankle Girth, inches	Skeletal measurements, inches												Fleshy measurements, inches												Body weight, pounds, per inch of Height
	Diameters					Girths							Diam.	Girths											
	Bi-acromial	Chest Trans.	Chest Ant.-post.	Bi-iliac	Bi-trochanteric	Wrist R.	Wrist L.	Knee R.	Knee L.	Ankle* R.	Ankle* L.		Bi-deltoid	Neck	Upper arm, flexed R.	Upper arm, flexed L.	Forearm R.	Forearm L.	Chest normal	Waist	Hips	Thigh R.	Thigh L.	Calf R.	Calf L.	
7.0	11.8	9.2	6.2	9.4	10.6	5.2	5.2	11.9	11.9	—	—		13.9	10.8	9.5	9.5	8.2	8.2	28.5	22.2	31.8	18.7	18.7	11.5	11.5	1.415
7.05	11.9	9.2	6.2	9.5	10.7	5.2	5.2	11.9	11.9	—	—		14.0	10.9	9.6	9.6	8.2	8.2	28.7	22.4	32.0	18.8	18.8	11.6	11.6	1.433
7.1	12.0	9.3	6.3	9.5	10.7	5.3	5.3	12.0	12.0	—	—		14.1	11.0	9.7	9.7	8.3	8.3	28.9	22.5	32.2	18.9	18.9	11.7	11.7	1.453
7.15	12.1	9.4	6.3	9.6	10.8	5.3	5.3	12.1	12.1	—	—		14.2	11.1	9.8	9.8	8.3	8.3	29.1	22.7	32.4	19.1	19.1	11.8	11.8	1.474
7.2	12.2	9.5	6.4	9.7	10.9	5.3	5.3	12.2	12.2	—	—		14.3	11.1	9.8	9.8	8.4	8.4	29.3	22.9	32.7	19.2	19.2	11.9	11.9	1.495
7.25	12.3	9.5	6.4	9.7	11.0	5.4	5.4	12.3	12.3	—	—		14.4	11.2	9.9	9.9	8.5	8.5	29.5	23.0	32.9	19.3	19.3	11.9	11.9	1.516
7.3	12.3	9.6	6.4	9.8	11.0	5.4	5.4	12.4	12.4	—	—		14.5	11.3	10.0	10.0	8.5	8.5	29.7	23.2	33.1	19.5	19.5	12.0	12.0	1.537
7.35	12.4	9.7	6.5	9.9	11.1	5.4	5.4	12.5	12.5	—	—		14.6	11.4	10.0	10.0	8.6	8.6	29.9	23.3	33.3	19.6	19.6	12.1	12.1	1.558
7.4	12.5	9.7	6.5	9.9	11.2	5.5	5.5	12.5	12.5	—	—		14.7	11.4	10.1	10.1	8.6	8.6	30.1	23.5	33.6	19.7	19.7	12.2	12.2	1.579
7.45	12.6	9.8	6.6	10.0	11.3	5.5	5.5	12.6	12.6	—	—		14.8	11.5	10.2	10.2	8.7	8.7	30.3	23.7	33.8	19.9	19.9	12.3	12.3	1.600
7.5	12.7	9.8	6.6	10.1	11.3	5.6	5.6	12.7	12.7	—	—		14.9	11.6	10.2	10.2	8.8	8.8	30.5	23.8	34.0	20.0	20.0	12.4	12.4	1.622
7.55	12.8	9.9	6.7	10.1	11.4	5.6	5.6	12.8	12.8	—	—		15.0	11.7	10.3	10.3	8.8	8.8	30.7	24.0	34.3	20.1	20.1	12.4	12.4	1.644
7.6	12.9	10.0	6.7	10.2	11.5	5.6	5.6	12.9	12.9	—	—		15.1	11.8	10.4	10.4	8.9	8.9	30.9	24.1	34.5	20.3	20.3	12.5	12.5	1.666
7.65	12.9	10.1	6.8	10.3	11.6	5.7	5.7	13.0	13.0	—	—		15.2	11.8	10.4	10.4	8.9	8.9	31.1	24.3	34.7	20.4	20.4	12.6	12.6	1.688
7.7	13.0	10.1	6.8	10.3	11.6	5.7	5.7	13.1	13.1	—	—		15.3	11.9	10.5	10.5	9.0	9.0	31.3	24.5	34.9	20.5	20.5	12.7	12.7	1.710
7.75	13.1	10.2	6.8	10.4	11.7	5.7	5.7	13.1	13.1	—	—		15.4	12.0	10.6	10.6	9.1	9.1	31.5	24.6	35.2	20.7	20.7	12.8	12.8	1.732
7.8	13.2	10.2	6.9	10.5	11.8	5.8	5.8	13.2	13.2	—	—		15.5	12.1	10.6	10.6	9.1	9.1	31.7	24.8	35.4	20.8	20.8	12.8	12.8	1.754
7.85	13.3	10.3	6.9	10.5	11.9	5.8	5.8	13.3	13.3	—	—		15.6	12.1	10.7	10.7	9.2	9.2	31.9	24.9	35.6	20.9	20.9	12.9	12.9	1.777
7.9	13.4	10.4	7.0	10.6	11.9	5.8	5.8	13.4	13.4	—	—		15.7	12.2	10.8	10.8	9.2	9.2	32.1	25.1	35.8	21.1	21.1	13.0	13.0	1.800
7.95	13.4	10.4	7.0	10.7	12.0	5.9	5.9	13.5	13.5	—	—		15.8	12.3	10.8	10.8	9.3	9.3	32.3	25.2	36.1	21.2	21.2	13.1	13.1	1.823
8.0	13.5	10.5	7.1	10.7	12.1	5.9	5.9	13.6	13.6	—	—		15.9	12.4	10.9	10.9	9.3	9.3	32.5	25.4	36.3	21.3	21.3	13.2	13.2	1.846
8.05	13.6	10.6	7.1	10.8	12.2	6.0	6.0	13.6	13.6	—	—		16.0	12.5	11.0	11.0	9.4	9.4	32.7	25.6	36.5	21.5	21.5	13.3	13.3	1.869
8.1	13.7	10.6	7.1	10.9	12.2	6.0	6.0	13.7	13.7	—	—		16.1	12.5	11.0	11.0	9.5	9.5	32.9	25.7	36.7	21.6	21.6	13.3	13.3	1.892
8.15	13.8	10.7	7.2	10.9	12.3	6.0	6.0	13.8	13.8	—	—		16.2	12.6	11.1	11.1	9.5	9.5	33.1	25.9	37.0	21.7	21.7	13.4	13.4	1.915
8.2	13.9	10.8	7.2	11.0	12.4	6.1	6.1	13.9	13.9	—	—		16.3	12.7	11.2	11.2	9.6	9.6	33.3	26.0	37.2	21.9	21.9	13.5	13.5	1.939
8.25	14.0	10.8	7.3	11.1	12.5	6.1	6.1	14.0	14.0	—	—		16.4	12.8	11.3	11.3	9.6	9.6	33.5	26.2	37.5	22.0	22.0	13.6	13.6	1.963
8.3	14.0	10.9	7.3	11.1	12.5	6.1	6.1	14.1	14.1	—	—		16.5	12.8	11.3	11.3	9.7	9.7	33.7	26.4	37.7	22.1	22.1	13.7	13.7	1.987
8.35	14.1	11.0	7.4	11.2	12.6	6.2	6.2	14.2	14.2	—	—		16.6	12.9	11.4	11.4	9.8	9.8	33.9	26.5	37.9	22.3	22.3	13.8	13.8	2.011
8.4	14.2	11.0	7.4	11.3	12.7	6.2	6.2	14.2	14.2	—	—		16.7	13.0	11.5	11.5	9.8	9.8	34.1	26.7	38.1	22.4	22.4	13.8	13.8	2.035
8.45	14.3	11.1	7.5	11.3	12.8	6.3	6.3	14.3	14.3	—	—		16.8	13.1	11.5	11.5	9.9	9.9	34.3	26.8	38.3	22.5	22.5	13.9	13.9	2.059
8.5	14.4	11.2	7.5	11.4	12.8	6.3	6.3	14.4	14.4	—	—		16.9	13.1	11.6	11.6	9.9	9.9	34.6	27.0	38.6	22.7	22.7	14.0	14.0	2.083
8.55	14.5	11.2	7.5	11.5	12.9	6.3	6.3	14.5	14.5	—	—		17.0	13.2	11.7	11.7	10.0	10.0	34.8	27.2	38.8	22.8	22.8	14.1	14.1	2.108
8.6	14.5	11.3	7.6	11.5	13.0	6.4	6.4	14.6	14.6	—	—		17.1	13.3	11.7	11.7	10.0	10.0	35.0	27.3	39.0	22.9	22.9	14.2	14.2	2.133
8.65	14.6	11.4	7.6	11.6	13.1	6.4	6.4	14.7	14.7	—	—		17.2	13.4	11.8	11.8	10.1	10.1	35.2	27.5	39.2	23.1	23.1	14.2	14.2	2.158
8.7	14.7	11.4	7.7	11.7	13.1	6.4	6.4	14.7	14.7	—	—		17.3	13.5	11.9	11.9	10.2	10.2	35.4	27.6	39.5	23.2	23.2	14.3	14.3	2.183
8.75	14.8	11.5	7.7	11.7	13.2	6.5	6.5	14.8	14.8	—	—		17.4	13.5	11.9	11.9	10.2	10.2	35.6	27.8	39.7	23.3	23.3	14.4	14.4	2.208
8.8	14.9	11.6	7.8	11.8	13.3	6.5	6.5	14.9	14.9	—	—		17.5	13.6	12.0	12.0	10.3	10.3	35.8	27.9	39.9	23.5	23.5	14.5	14.5	2.233
8.85	15.0	11.6	7.8	11.9	13.4	6.6	6.6	15.0	15.0	—	—		17.6	13.7	12.1	12.1	10.3	10.3	36.0	28.1	40.2	23.6	23.6	14.6	14.6	2.258
8.9	15.0	11.7	7.9	11.9	13.4	6.6	6.6	15.1	15.1	—	—		17.7	13.8	12.1	12.1	10.4	10.4	36.2	28.3	40.4	23.7	23.7	14.7	14.7	2.284
8.95	15.1	11.8	7.9	12.0	13.5	6.6	6.6	15.2	15.2	—	—		17.8	13.8	12.2	12.2	10.5	10.5	36.4	28.4	40.6	23.8	23.8	14.7	14.7	2.310
9.0	15.2	11.8	7.9	12.1	13.6	6.7	6.7	15.3	15.3	—	—		17.9	13.9	12.3	12.3	10.5	10.5	36.6	28.6	40.8	24.0	24.0	14.8	14.8	2.336
9.05	15.2	11.9	8.0	12.1	13.7	6.7	6.7	15.3	15.3	—	—		18.0	14.0	12.3	12.3	10.6	10.6	36.8	28.7	41.1	24.1	24.1	14.9	14.9	2.362
9.1	15.4	11.9	8.0	12.2	13.8	6.7	6.7	15.4	15.4	—	—		18.1	14.1	12.4	12.4	10.6	10.6	37.0	28.9	41.3	24.3	24.3	15.0	15.0	2.388
9.15	15.5	12.0	8.1	12.3	13.8	6.8	6.8	15.5	15.5	—	—		18.2	14.2	12.5	12.5	10.7	10.7	37.2	29.1	41.5	24.4	24.4	15.1	15.1	2.414
9.2	15.6	12.1	8.1	12.3	13.9	6.8	6.8	15.6	15.6	—	—		18.3	14.2	12.5	12.3	10.7	10.7	37.4	29.2	41.7	24.5	24.5	15.2	15.2	2.441
9.25	15.6	12.1	8.2	12.4	14.0	6.8	6.8	15.7	15.7	—	—		18.4	14.3	12.6	12.6	10.8	10.8	37.6	29.4	42.0	24.7	24.7	15.2	15.2	2.468
9.3	15.7	12.2	8.2	12.5	14.1	6.9	6.9	15.8	15.8	—	—		18.5	14.4	12.7	12.7	10.9	10.9	37.8	29.5	42.2	24.8	24.8	15.3	15.3	2.495
9.35	15.8	12.3	8.3	12.5	14.1	6.9	6.9	15.8	15.8	—	—		18.6	14.5	12.8	12.8	10.9	10.9	38.0	29.7	42.4	24.9	24.9	15.4	15.4	2.522
9.4	15.9	12.3	8.3	12.6	14.2	7.0	7.0	15.9	15.9	—	—		18.7	14.5	12.8	12.8	11.0	11.0	38.2	29.9	42.6	25.1	25.1	15.5	15.5	2.548

*Same as "corrected" ankle girth.

Table B (Female).

experienced in the use of this method; 4 and 5 were not. The results are shown in Table C. The maximum variation in one subject was six pounds; in three subjects, four pounds; and in one subject, only two pounds. I believe this is no greater variation than five technicians would get in almost any laboratory procedure.

Clinical Possibilities. One should not teach that obesity is a menace to health and longevity unless one is willing to accept the responsibility of its prevention, or at least of its cure. The fact that probably only a small per cent of overweight individuals have an endocrine etiology is beside the point. Sufferers from this disorder are seeking the advice of the endocrinologist in rapidly increasing numbers. It behooves him not only to make a differential diagnosis but to institute an intelligent therapeutic or dietary regime. Except in rare instances, obesity is insidious. A gain of from 10 to 20 per cent in weight every year is not unusual. The condition should be recognized in its incipience, not after the indi-

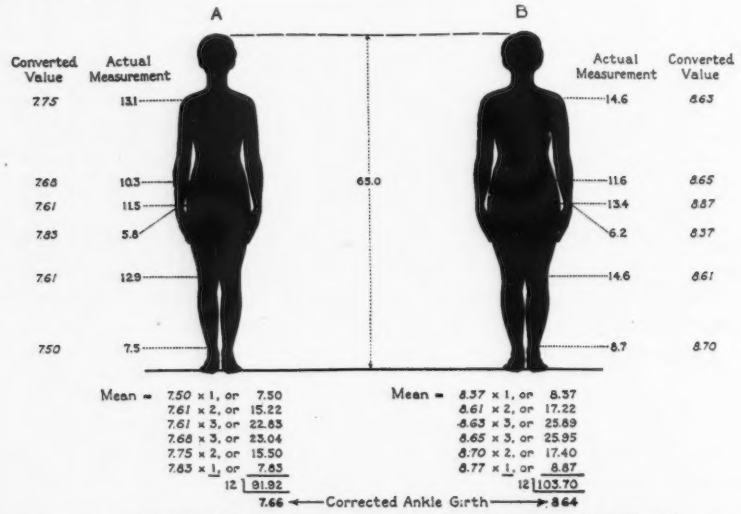
vidual is markedly overweight. Just why some persons gain up to a certain high figure and remain there, apparently irrespective of food intake or energy output, is not known. Suffice it to say, that many do not. The

TABLE C

WEIGHT OF FIVE SUBJECTS ESTIMATED INDEPENDENTLY BY FIVE EXAMINERS

Subject	Examiner					Greatest Variation, Pounds
	1	2	3	4	5	
A	155	155	156	157	153	4
B	119	120	118	120	120	2
C	138	140	136	137	138	4
D	149	147	149	150	146	4
E	117	119	118	123	122	6

trend is usually upward until something foreign to the balancing mechanism itself intervenes.



Extract from Tabulation

	Corrected Ankle Girth, inches	Skeletal Measurements, inches								Fleshy Measurements, inches								Body weight, pounds per inch of height
		Diameters				Girths				Diam	Girths							
		Bi-acromial	Chest Trans	Chest Ad-sag	Bi-iliac	Bi-trochanteric	Wrist	Knee	Ankle	Bi-deltoid	Neck	Upper Arm, flexed	Forearm	Chest, normal	Waist	Hips	Thigh	Calf	
A	7.66	13.0	10.1	6.8	10.3	11.6	5.7	13.0	—	13.2	11.8	10.4	8.9	31.1	24.3	34.7	20.4	12.6	1.692
B	8.64	14.6	11.4	7.6	11.6	13.1	6.4	14.7	—	17.2	13.4	11.8	10.1	35.2	27.5	39.2	23.1	14.2	2.153

Therefore, A's weight = 65 × 1.692, or 110 pounds: B's weight = 65 × 2.153, or 140 pounds

Chart III

Comparison of (A) small boned woman with (B) large boned woman of the same height. Showing how different optimal weights may be estimated.

Take, for example, a young woman of 20, 65 inches in height and moderately overweight. She has learned through semi-scientific reading and perhaps the experiences of friends that overweight, aside from being a cosmetic misfortune, is also a physical handicap. Armed with this knowledge she consults a physician. The consideration which she receives, depending upon the physician, ranges anywhere from a careful examination to an indulgent smile. Usually it is the latter. Without inquiring

TABLE D
Showing Variations In Weight Tables
EXTRACTS FROM WEIGHT TABLES
WOOD
Average Weight and Height of Girls of Different Ages

Height (inches)	5 Yrs.	6 Yrs.	7 Yrs.	8 Yrs.	9 Yrs.	10 Yrs.	11 Yrs.	12 Yrs.	14 Yrs.	14 Yrs.	15 Yrs.	16 Yrs.	17 Yrs.	18 Yrs.	19 Yrs.	20 Yrs.
63	..	..	..	..	..	..	..	..	..	107	109	116	110	112	113	114
64	..	..	..	..	..	.	..	..	..	112	118	116	117	114	119	115
65	..	..	..	..	..	..	..	..	..	114	118	121	125	120	123	125

Taken from the ninth Yearbook of the National Society for the Study of Education: Part I—Health and Education, by Thomas Denison Wood, M.D.

LIFE EXTENSION INSTITUTE
Correct Weight According to Height

WOMEN			MEN		
Height		Weight, Pounds	Height		Weight, Pounds
Feet	Inches		Feet	Inches	
5	3	127	5	8	152
5	4	130	5	9	156
5	5 (65)	134	5	10	161

METROPOLITAN LIFE INSURANCE COMPANY
Women
Weights According to Age Period

Height		20 to 24 Years	25 to 29 Years	30 to 34 Years	35 to 39 Years	40 to 44 Years	45 to 49 Years	50 to 54 Years	55 to 59 Years
Feet	Inches								
5	3	123	125	128	132	136	139	141	143
5	4	126	129	132	136	139	142	144	146
5	5 (65)	129	132	136	140	143	146	148	150

into the annual weight increment, the caloric intake and energy output, the family history or her other complaints, if any, and almost certainly without benefit of a proper physical examination, she is relegated to the large family of neurotic, fashion-ridden girls.

Occasionally the physician is right; frequently he is wrong. It is not uncommon to find a woman 75 to 100 per cent overweight who, when

younger, suffered caustic lectures from her medical adviser on the foible of reducing. At a time when simple instruction and careful observation could have prevented such a misfortune, she is ridiculed into a life of unhappy redundancy. In my opinion, this is not so much negligence as it is confusion, which arises through a misunderstanding of what constitutes the patient's optimal weight. By consulting the Wood Table one finds that the average young woman 20 years of age and 65 inches in height weighs 125 pounds. According to the Life Extension Institute Table, she

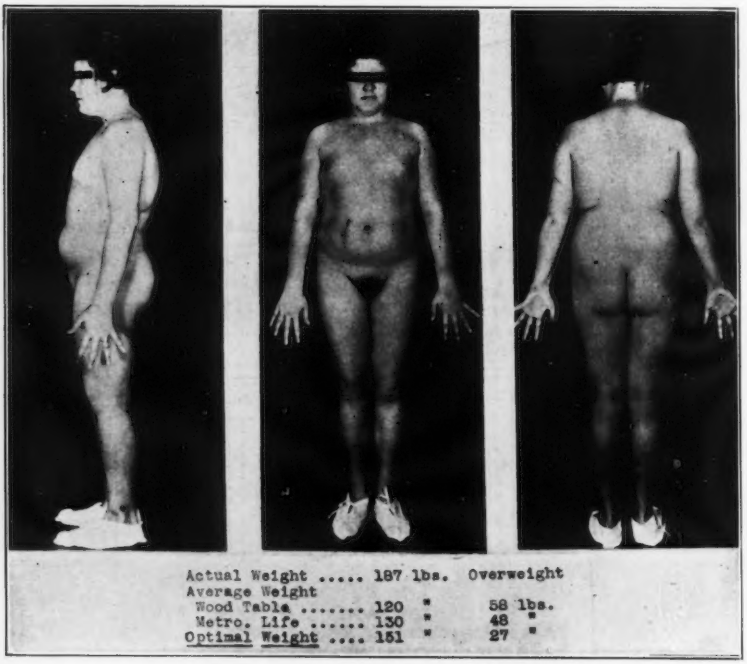


FIGURE 2

should weigh 134 pounds; and according to the Metropolitan Life Table, 129 pounds. Assuming that an 8-pound variation either way in any of these tables is compatible with reason, this same girl could weigh from 117 to 133 pounds, according to the Wood Table, and from 126 to 148 pounds, according to the Life Extension Institute Table, a maximum variation of 25 pounds. Which figure should one choose? I have known many young women of this age and height who were actually emaciated at 117 pounds and others who were obese at 142. Of course, the contention will be that clinical judgment is adequate in optimal weight estimation, but I maintain that casual observation in this, as in every other branch of medicine, only lends itself to confusion. Every individual has a weight which befits his

bony framework. If there is a means whereby this may be more accurately estimated, it should be employed.

We have used the Willoughby Method both in private practice and in our clinics at the St. Francis and Cottage Hospitals for nearly two years. During this period several hundred patients have been examined. Our interpretation of this "ideal" individual weight is always tempered by judgment. We realize that many persons long overweight can never be completely rehabilitated because of some physical infirmity, or because of poor cosmetic effect. Of the former I may say, however, that few overweight persons do not profit by an intelligent reduction regime; of the latter, that the elasticity of redundant tissue is much greater than many suspect. I have repeatedly seen young women lose as much as 80 pounds without the slightest cosmetic deformity. Be that as is may, the method is more useful in the adolescent or young adult and those at any age not excessively overweight. Here an individual weight not only affords the patient an ideal to acquire and maintain, but, by taking the matter out of the realm of empiricism, it stimulates the physician to a much better effort. The method is equally informative in underweight where, by insulin therapy or other means, the observer attempts to build the patient up to the most effective poundage.

The following case reports will suffice to show the usefulness of this method as employed by us.

E. H., age 16, the daughter of a very obese, large-boned woman had been told repeatedly that she was from 50 to 60 pounds overweight. Despairing, she refused to attempt rehabilitation and sullenly prepared to go the way of her mother. The patient's actual weight was found to be 187 pounds. According to the Wood Table, she was 58 pounds overweight; according to the Metropolitan Life Table, she was 48 pounds overweight. We found her only 27 pounds overweight according to the Method of Willoughby. A casual study of the photographs will show our calculation to be more likely correct. Laboratory and physical examination revealed no evidence of an endocrinopathy. The patient entered into the spirit of rehabilitation and dietary re-education with avidity. (See Fig. 2, page 502.)

J. H., age 12 years 5 months, consulted us Dec. 20, 1930. The complaints were obesity, somatopsychic behaviorisms and genital hypoplasia. The average of six basal metabolic rate estimations was —22 per cent, the highest being —19.6 per cent, and the lowest —25.2 per cent. All other laboratory and x-ray findings were essentially normal. The actual weight was 173.7 pounds. The estimated optimal weight according to method of Willoughby was 110 pounds, or 63.7 pounds lower. The treatment was directed toward the lowered metabolism by the addition of one grain of thyroid daily and toward the genital hypoplasia by hypodermic administration of anterior pituitary sex fractions. The patient was placed on a 1200 calorie diet. On Dec. 26, 1931, he weighed 140 pounds. Re-estimation on this date revealed his optimal weight to be 132.1 pounds. Thus, he was only 7.9 pounds overweight. His height was 63.5 inches. (See Fig. 3, page 504.)

I shall not enter into a discussion as to what brought about this result. Normal adolescence was undoubtedly a factor. We have many patients, however, past the adolescent period in whom nature has made a dismal failure. No matter what the physiologic level for the deposition of fat, dietary re-education is an essential feature of the cure. The point in question is not one of etiology or therapy, but one of weight. Tables por-

tending to show that a child this age should gain only six to eight pounds per year are now in use. We believe they are relatively of little value. From re-estimations, it appears that this patient should have gained ap-

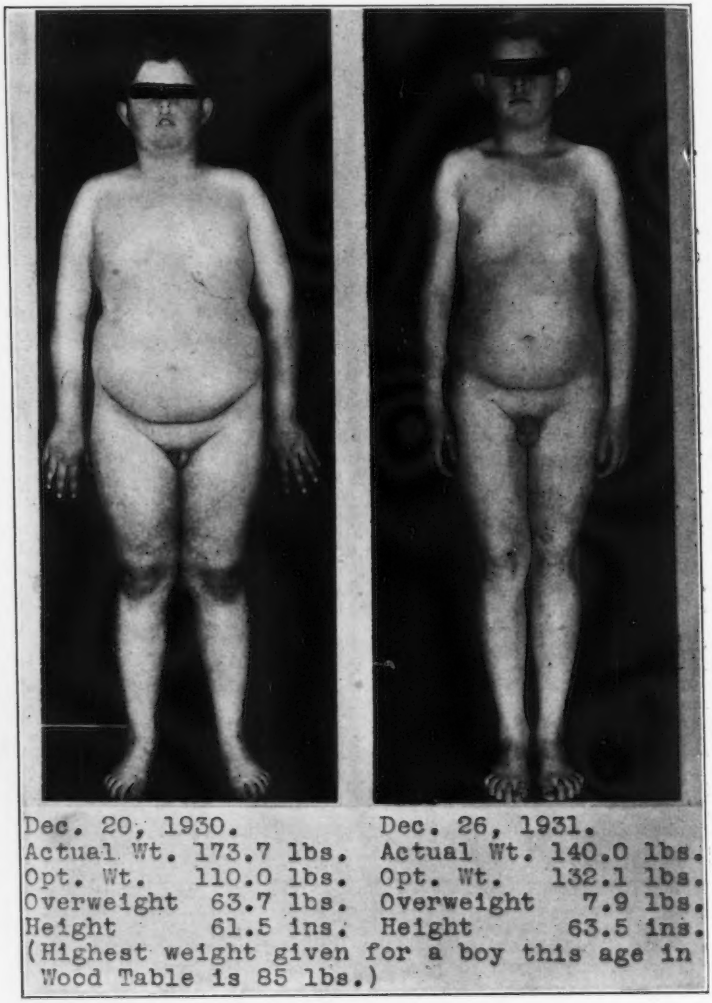

Dec. 20, 1930.
Actual Wt. 173.7 lbs.
Opt. Wt. 110.0 lbs.
Overweight 63.7 lbs.
Height 61.5 ins.
Dec. 26, 1931.
Actual Wt. 140.0 lbs.
Opt. Wt. 132.1 lbs.
Overweight 7.9 lbs.
Height 63.5 ins.
(Highest weight given for a boy this age in Wood Table is 85 lbs.)

FIGURE 3

proximately 22 pounds during the year. Therefore, the rehabilitation in growing children does not consist of reduction to the originally estimated level but to the level at which they should be when treatment is discontinued.

SUMMMARY

A new method of optimal weight estimation (that of Willoughby) is herein described. It is based upon the theory that weight should be in direct ratio to skeletal size or thickness, irrespective of age. At present only its applicability to adults has been demonstrated.

Six skeletal measurements are employed from which by a simple computation, the optimal (theoretically ideal) weight is derived.

The author has used the method for more than two years. It is believed to have distinct advantages over the height-weight-age scales now in use and to be conducive to better management of the weight problem in clinical practice.

Although there are many technical difficulties to be surmounted in the ultimate perfection of such a method, it is considered of sufficient importance to warrant careful study.

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THE ACTION OF EXTRACTS OF ANTERIOR PITUITARY AND OF PREGNANCY URINE ON THE TESTES OF IMMATURE RATS AND MONKEYS*

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Several score of papers dealing with the action of extracts of pregnancy urine and of the anterior pituitary on the male genital system bear witness to the attention which has been focused on this point since 1927. In our earlier work on the effect of implants (Smith and Engle), we noted that the distinct growth of the seminal vesicles of implanted animals demonstrated an activity of the interstitial cells, though morphological changes were not directly observable on these cell bodies.

These observations have been greatly extended by many investigators,[1] who note varying degrees of hypertrophy and hyperplasia in the interstitial cells after treatment with extracts of anterior pituitary or pregnancy urine. With the exception of the report of Balawenetz (1930), no one has reported success in hastening the formation of spermatids or spermatozoa in an immature male mammal, and it is generally agreed that, in the male at least, none of these gonad-stimulating factors are directly concerned with gametogenesis.

These accumulated observations on the prepubertal male emphasize the position taken a year ago in regard to the action of anterior pituitary principles on the female (Engle, 2). We are dealing with a genital acceleration mainly of the hormone producing structures but have not produced true precocious puberty. That phenomenon is more complex than may be explained by the action of a single hormonal factor.

The condition in the fowl is different than the mammal, for the male gonad of the duck gives an indubitable response with germ cells having mature form, while the ovary is relatively unaffected (Schockaert, 1931).

The present report presents the data obtained by treatment of immature rats with the water-soluble fraction of sheep anterior lobe and with concentrated pregnancy urine. No particularly new concept has been derived from these experiments on the rats, and the data and conclusions are presented more as a review of the present status of the anterior-pituitary-testis problem and to give a background for new work with monkeys.

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Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 9, 1932.

[1]An extensive literature has been discussed by the author in the forthcoming "Internal Secretions and Sex," edited by Edgar Allen. Williams & Wilkins, Baltimore, 1932. For this reason extensive citations have not appeared in this text.

Experimental Procedures: The method of pyridine extraction of powdered sheep pituitary developed by Fevold, Hisaw and Leonard (1931) has been found suitable in producing a good follicular-stimulating factor when tested on female rats, mice and monkeys. The material was prepared so that 30 cc. of the water soluble factor contained the activity removed from 10 grams of dried powder of sheep pituitary.[2]

The pregnancy urine was precipitated with alcohol and the residue extracted five or six times with ether. The active principle was taken up in water, adjusted to pH 7.3 or 7.4. This has been found to be practically oestrin free and has given no positive Allen-Doisy test. In the concentrations used each cubic centimeter represents activity from 40 c.c. of pooled pregnancy urine of the first 5 months of gestation. This has not been standardized in mouse or rat units, nor is it believed that the extraction has been quantitative, although each lot has approximately the same degree of potency when tested on immature female rats.

Littermate male rats were treated with these two preparations, the data being summarized in table 1. The testis weights of the pyridine-

TABLE I

RESPONSE OF RAT TESTES TO INJECTIONS OF ANTERIOR PITUITARY (PYRIDINE EXTRACT) AND PREGNANCY URINE CONCENTRATE

Number Animal	Experiment Begun				Experiment Terminated				
	Age Days	Body Weight, gms.	Treatment Daily	Number Days	Age Days	Body Weight, gms.	Weight of Both Testes mgs.	Length Sem. Ves., mm.	Testis Ratio
6915	30	44	Control	0	40	68	234.7	4.5	1.00
6916	30	48	1/10 APx2	10	40	75	445.0	7.2	1.90
6917	30	50	1/3 PUx2	10	40	68	330.1	8.5	1.41
6921	30	46	2/10 APx2	10	40	72	492.3		2.10
6935	24	58	Control	0	34	76	369.6		1.00
6936	24	57	1/10 APx2	10	34	66	871.7		2.36
6937	24	52	1/3 PUx2	10	34	62	490.5		1.32
6943	27	44	1/10 APx2	10	37	60	630.0	6.7	1.03
6944	27	42	1/10 APx2	10	37	61	567.0	4.7	0.92
6945	27	44	Control	0	37	64	609.9	4.9	1.00
6946	27	42	1/10 PUx2	10	37	52	520.0	7.8	0.85
6947	27	45	1/10 PUx2	10	37	58	782.0	8.7	1.28
6981	21	29	1/4 APx2	6	30	36	295.0		
6983	21	27	1/6 APx2	8	30	30	226.4		
6984	21	30	Control	0	33	44	238.6	4.1	1.00
6985	21	28	1/8 APx2	12	33	52	593.9	6.6	2.49
6987	22	34	1/10 APx2	10	33	44	591.8	7.6	2.48
7116	25	44	1/4 APx2	10	35	68	821.4	5.7	1.91
7114	25	39	1/4 Sheep P	10	35	76	738.0	6.9	1.74
7113	25	44	1/4 PUx2	10	35	73	660.5	10.0	1.54
7112	25	44	Control	0	35	65	428.7	5.1	1.00

extract treated animals is greater than those of the animals treated with pregnancy urine, and both are considerably above the control weights. The control testis weights being one, the average testis weights of the A.P. treated rats is 1.98 and the P.U. treated 1.28. Similarly, the tubules in

[2]The powdered sheep pituitary glands were furnished by Parke Davis & Co., through the courtesy of Dr. O. P. Kamm.

both treated series are larger in diameter than the controls, although there does not appear to be a uniform difference between the two groups of animals which had received the two types of treatment. A small number of fields were measured with a planimeter on projection tracings. Only those tubules were measured in which the plane of section had passed at a right angle to the tubule. The range of size of tubules of the treated animals showed much overlap between the two groups, but were uniformly higher than the untreated control. It is not possible at this time to assign a different range of tubule growth between the animals treated with anterior lobe extract or pregnancy urine. Tubules are larger than the controls after either treatment.

Within the tubules much the same histological reactions have occurred as have been described previously (Engle, Boeters, Borst, Neumann, Kraus). The obvious result is that neither spermatids nor spermatozoa have occurred earlier than in the controls. In some cases mitoses appear unaffected under either type of treatment, while in other animals extensive degeneration may have occurred, with large clumped cell masses free in the lumen. This has occurred in both A.P. and P.U. treated animals. This is a condition described by Maximow (1899) as occurring after testis injury and in aged men. In my experience the cellular destruction has not been related to a difference in dosage or length of treatment.

The most constant and marked difference between the testis after anterior lobe treatment and after injections of pregnancy urine is in the interstitial cell mass (Figs 1, 2, 3). It was noticed by Smith and Engle that an increase of the interstitial cell mass after implants did not occur, but that the accessory apparatus did show great increase in size and development, from which evidence it was assumed that the activation occurred through interstitial cells without observable morphological changes occurring in this tissue. In animals treated with pyridine extract much the same phenomenon occurs. The relative increase in the volume of cells is somewhat greater than in the control, while the accessory glands have greatly increased in volume. There appears, however, a much greater increase in the interstitial cell mass of the testis after treatment with pregnancy urine than with pyridine extract of the gland. Neither of these extracts have been titered in mouse units, but it is felt that the difference mentioned here is not the result of a difference in available active principle. The ratio of increase in P.U. treated animals over the A.P. injected is several times greater than the ratio of the A.P. treated over the control. However, the seminal vesicles of both types of animals show approximately a two-fold increase over the controls, irrespective of the volume of interstitial tissue.

The immature monkey has also been used in this series.[3] The relevant

[3]Several of the monkeys used in this series were animals which had been used previously in neutralization tests for the virus of poliomyelitis in experiments of Dr. C. W. Jungeblut and the author, and were kindly given for this work by Dr. Jungeblut.

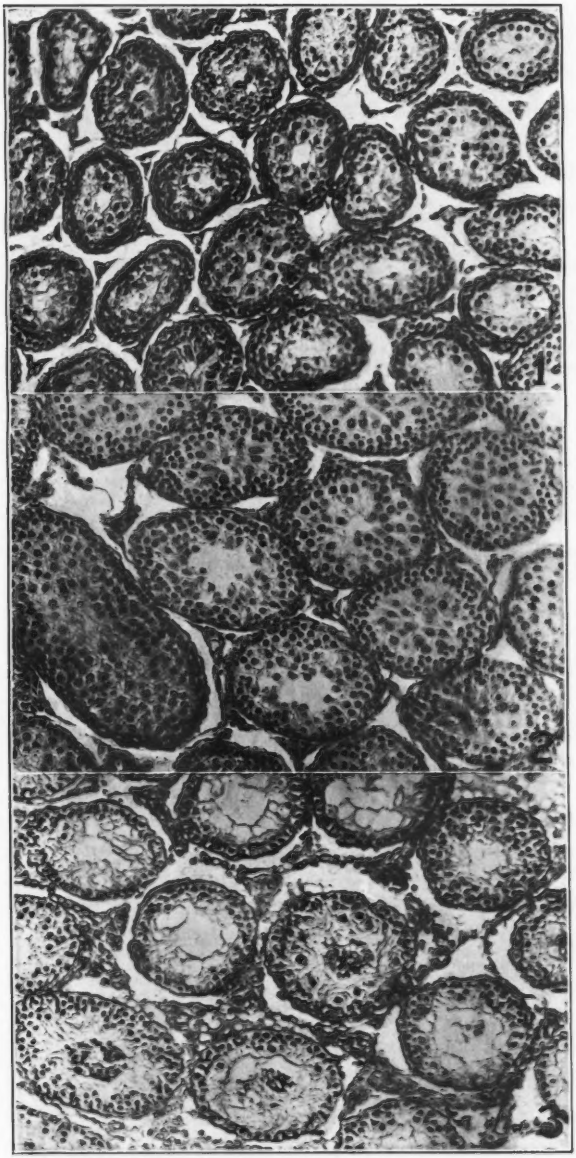

Figure 1. Testis of Rat No. 6915, 40 days of age, untreated littermate control of 6916 and 6917.

Figure 2. Testis of Rat No. 6916. Ten days treatment with anterior pituitary extract.

Figure 3. Testis of Rat No. 6917. Ten days treatment with aqueous extract of pregnancy urine.

TABLE II

ANTERIOR PITUITARY AND PREGNANCY URINE ON IMMATURE MALE MONKEYS (MACACUS)

No. Monkey	Experiment Started					Experiment Closed	
	Body Weight, gms.	Control Testis		Treatment		Exper. Testis	
		Weight, mgs.	Size, mm.	Dosage	Days	Weight, mgs.	Size, mm.
My 66	3300	R	10	AP 35 cc. = 10.6 gms.	15	L 897	16.0x11.4x 9.8
67	2950	R	10.4	AP 73 cc. = 24.3 gms.	21	L 511	14.2
72	2950	R 238	10.0x 7.5x6.6	AP 73 cc. = 24.3 gms.	14	L 476	13.0x 9.1x 8.5
73	3650	R 374	11.0x 7.9x6.8	AP 70 cc. = 23 gms.	29	L 808	15.8x10.0x 8.7
81	3850	L 815	16.9x10.7x9.4	PU 30 cc. 1:50 = 1500 cc.	20	R 1548	18.7x14.9
85	2650	R 313	11.0x 7.7x7	PU 43 cc. 1:40 = 1720 cc.	27	L 707	13.5x10.7x 9.9
86	3800	R 581	13.3x 9.0x7.6	PU 40 cc. 1:40 = 1600 cc.	24	L 1279	17.6x13.0x11.4

data are assembled in Table II. The same preparations have been used with the monkeys as with the rats discussed above. Lacking littermate controls, recourse has been had to unilateral controls. The testis and seminal vesicle of one side were removed, and after an interval of a few days injections were begun. It is generally accepted that little if any compensatory hypertrophy occurs after unilateral castration and in these studies no allowance is made for this factor.

The same type of differences occurs in the monkey that occurs in the rat. The seminiferous tubules after treatment increase more than two times the size of those of the control testis, and the increase of the interstitial tissue is greater in the monkey which received the pregnancy urine than those receiving anterior pituitary extract (Figs. 4 and 5). In no case, however, has any extensive erosion of the germinal epithelium occurred as is occasionally seen in the rat. The weight of the treated testis, after removal of a control, has uniformly increased in size and the weights are doubled following a period of treatment.

The seminal vesicles and prostate of monkeys treated with pregnancy urine are very greatly enlarged over the control, being as large as the organs of adult monkeys of three times the body weight which I have examined. The size of the accessory organs of the A.P. treated animals is considerably greater than the control, but does not equal the condition following injection of pregnancy urine. Morphological details of these findings will be presented elsewhere.

SUMMARY

Data are reported on the effects in the testes of 16 immature rats and seven monkeys of extracts of anterior pituitary gland or of pregnancy urine. An increase in testis size was noted. This was due to an increased

tubule growth and to an increase in the interstitial cell mass. In the monkey the weight and size increase was uniform and pronounced. In the rat it was not so uniform. No acceleration in gametogenesis occurred in either animal after treatment.

The increase in the interstitial cell mass appeared greater after treatment with pregnancy urine than with anterior lobe extract.

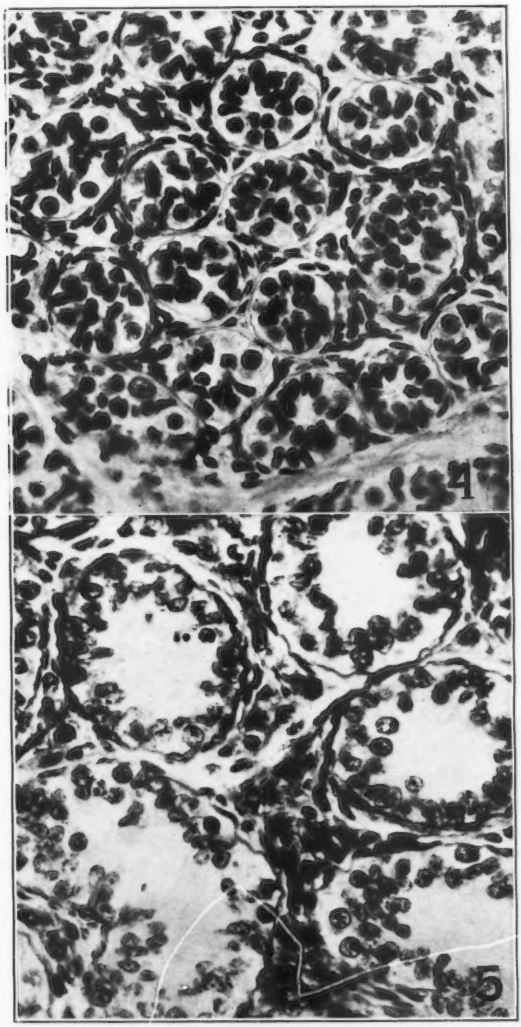

Figure 4. Left testis of monkey, My 81, removed before treatment.
Figure 5. Right testis of My 81, after twenty days treatment with extract of urine of pregnancy, equivalent to 1720 c.c. of whole urine.

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EXPERIMENTALLY INDUCED DESCENT OF THE TESTIS IN THE MACACUS MONKEY BY HORMONES FROM THE ANTERIOR PITUITARY AND PREGNANCY URINE

THE ROLE OF THE GONADOKINETIC HORMONES IN PREGNANCY BLOOD IN THE NORMAL DESCENT OF THE TESTES IN MAN*

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The response of the testes of immature rats and monkeys to injections of pregnancy urine and anterior pituitary have been discussed in the preceding paper. The present report emphasizes one phase of the response in the Macacus monkey, together with an interpretation of its relation to human biology.

Little is known about the size or age of the male Macacus monkey at sexual maturity, but the animals used in this study were still very considerably below the advent of puberty. Littermate or age-weight controls cannot be obtained with monkeys. Therefore, unilateral organ controls were obtained in several animals by operative removal of one testis and a portion of one seminal vesicle. After a post-operative interval of several days, treatment with either pyridine extract of anterior pituitary or the water soluble fraction from pregnancy urine was begun.†

In these immature males, whether the animal weighs 2500 grams or 4400 grams, the testes are located in the upper portion of the inguinal ring (Fig. 1). The internal ring is closed, and the testis cannot be retracted into the abdomen by traction on the spermatic cord. While the testes vary in size with the size of the animal, they are relatively inconspicuous though readily located bodies. A testis in this location is moveable in the canal on palpation for about the length of the testis, or roughly about one-third of the length of the canal. As is shown in Figure 1, the scrotum is a flattened extension of the skin, which is relatively inconspicuous. In a large series of monkeys which have been handled by myself and my colleagues, no one has been encountered in which the testes were resident in the scrotum, nor could be moved into the scrotum by manipulation, though the animals have ranged as high as 4.5 kilos in weight. A female monkey begins to menstruate at a body weight of about 3.5 kilos,

*Read before the sixteenth annual meeting of the Association for the Study of Internal Secretions, New Orleans, May 9, 1932.

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†The urine of pregnancy was obtained from Sloane Hospital for Women, through the courtesy of the Director, Dr. B. P. Watson.

The dried sheep pituitary was furnished by Parke Davis & Co., through the courtesy of Dr. O. P. Kamm.

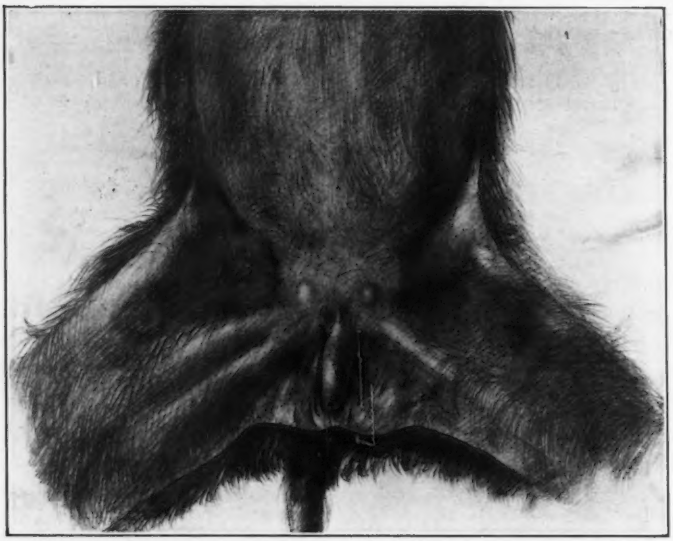

Figure 1. Immature monkey, 3000 gms. showing testes in the inguinal canal, and small scrotum.

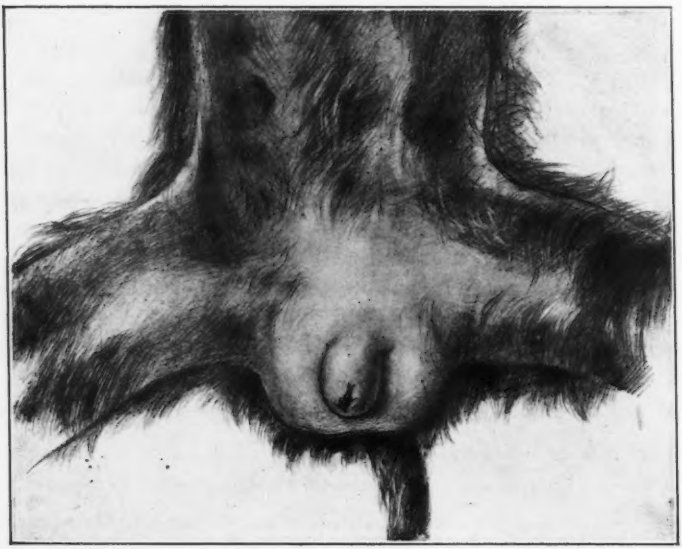

Figure 2. After treatment for 16 days with aqueous extract of pregnancy urine. The scrotal and peripenile turgescence is characteristic of this treatment. The testes are well placed in the scrotum.

and the male is probably about one kilo heavier during the period of puberty.

During treatment with either of the two extracts under discussion, the size of the testis is noticeably increased by the tenth day, an increase which continues during the course of the short three or four week period of the experiment.

When the weight of the testis which was removed before initiation of the treatment is compared with the weight of the one removed after treatment, it is found to be approximately doubled in size, regardless of the weight or size at the beginning of the experiment (Fig. 3).

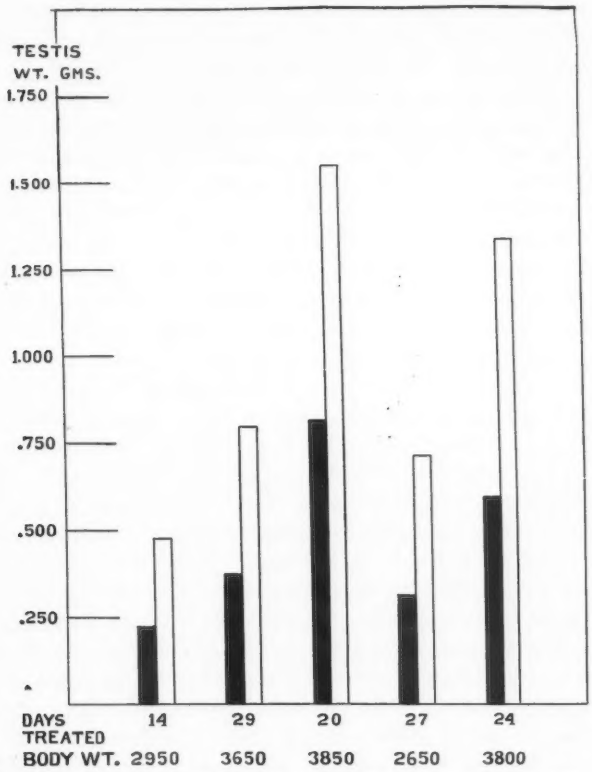

Figure 3. Diagram showing the weight of the control testis (black column), operatively removed before institution of treatment, and the weight of the remaining testis (blank column) after treatment.

At the same period (10 to 14 days) at which a perceptible increase in the size of the testis was noted, there was also seen a greater range in mobility of the organ. In larger animals after a fourteen-day treatment the testis usually rests in the canal at the level of the base of the penis or in the neck of the scrotum.

Especially noticeable during the course of injections was the change in the size and shape of the scrotum. After injections of either extract, the scrotum showed an increasing fullness, and even before the testis was within the scrotal sac, it had assumed a size and fullness comparable to that obtaining in a much larger animal.

This scrotal growth was slight after injections with extracts of the anterior lobe tissue, but it was quite dramatic after injections of extracts of pregnancy urine. After a few days of growth, the scrotal and peripenile area became turgescent and attained relatively large proportions, the scrotal skin becoming stretched and taut. The scrotal sac was filled with a mucoid-like tissue, on gross examination being quite similar to Wharton's jelly of the umbilical cord. In no case was there free fluid nor other similarity to a hydrocele. The scrotal change is dependent on the presence of the testis. A castrate male of 3900 grams was injected for 25 days with pregnancy urine extract with no scrotal change.

During the period of increase in size and the turgescence of the scrotum, together with the increasing growth of the testes, the testis moves from its position at the head of the inguinal canal into the scrotum.

This process is seen first as an increase in mobility and range of movement in the canal, and in progressive stages, leads to a normal position of the testis in the scrotum. This descent of the testis to the scrotum, where it rests when the animal is in a normal free position, has been best secured after treatment with extracts of pregnancy urine. In 10 monkeys used, ranging in body weight from 2650 grams to 4400 grams, complete descent has been secured in all but two cases if the period of treatment has been of sufficient length. In one of these cases, surgical sequelae following operative removal of the seminal vesicle accounted for a failure of complete descent. In the other one, the testes descended into the scrotum, but an increase in the tissue content of the scrotum, and an excessive turgidity evidently forced the testis back into the neck of the scrotum, where it rested just below the level of the base of the penis. This animal was not studied further, but was sacrificed to obtain necessary histological specimens.

Histologically the same conditions were observed in the testis that have been described before in the rat. The tubules increase in diameter, and in the monkeys treated with pregnancy urine a pronounced increase occurs in the interstitial tissue. In no monkey has there been observed the degeneration of seminal epithelium with the mass clumping of cells in the lumen of the tubules which has been described in the rat (Boeters), and likewise no hastening of spermatogenic activity. The action of the gonadokinetic factor of the anterior pituitary is primarily on the hormone producing structures and appears not to be directly concerned with accelerated gametogenetic maturity in either the male or female mammal.

On experimental grounds, therefore, it is clearly demonstrated that, in monkeys which have a relatively delayed appearance of puberty and with inguinal canals which normally close, the descent of the testis may be

experimentally induced by an active principle of the anterior pituitary or better by a similar, though possibly not identical, principle obtained from urine of pregnancy.

HORMONAL FACTORS ACTING ON THE GENITAL SYSTEM OF HUMAN FOETUSES

Halban in 1904 described changes in the genital organs of new born infants of both sexes which he ascribed to the action of certain then hypothetical internal secretions of the placenta. The evidence and the arguments were convincing, but the active principles involved were not made clear until the female sex hormone was demonstrated to be present in the placenta and the blood of pregnant women by Frank and Goldberger in 1926 and the presence of anterior lobe like substances in placenta and urine by Aschheim and Zondek in 1928.

With this knowledge of two genitokinetic factors in the placenta, and in the blood and urine of pregnant women it became possible to revive and review the observations of Halban and many others and to interpret them in the light of recent knowledge of hormone actions. This has been done by Neumann (1930) and by Engle (1932.)

In the male foetus and new born, Halban demonstrated a prostatic hypertrophy which underwent a natal involution, but he did not examine in detail the testes of these bodies. Reiprich (1925) and Neumann have reported on the histological changes of the foetal and new born testis. Neumann points to certain regressive changes in the seminiferous tubules at birth, which he attributes to the continued anti-masculine action of the female sex hormone, which is at a high concentration at this period. Reiprich found an increase in the interstitial cells from the ninth lunar month, with smaller and shrunken tubules, but at birth the interstitial-tubular ratio was reported to be more like that of the sixth month. These observations were largely confirmed by Neumann, who also reported that at birth a regression in the relative proportion of interstitial cells was already occurring and he rarely found them in large masses.

In the light of experimental data on the activation of the interstitial cells by the active anterior pituitary like substances found in blood, urine and the placenta of pregnant women, these findings assume significance for the present problem. According to Zondek's early estimates, the fall in concentration of these gonad-activating principles occurs in the last trimester of pregnancy, when the oestrin level is increasing. It is also known that both active principles are recovered from the blood and urine of new born infants, and from the urine at least to the fourth or sixth day of life [Philip (1929), Neumann, et al.].

The labial and scrotal swellings in the human new born, which subside within a week or so after birth, should be interpreted in the light of experiments on monkeys to be due to at least one of the two hormones known to occur during human pregnancy.

The swelling of the vulva, cutaneous turgescence and pachydermatous circumgenital reddening in the adult female macaque, the cynamolgous baboon and the chimpanzee which preceed the beginning of the menstrual flow have been repeatedly induced in castrated adult or immature female monkeys by injections of oestrin, or by ovarian activation secondary to injections of the gonadokinetic principle of the anterior pituitary. This has not occurred in any female in our colony after injections of pregnancy urine extract, and is regarded in the female as being due to oestrin. In the male macaque, however, the scrotal turgidity described above has followed injections of pregnancy urine, and less after anterior pituitary extracts; it is thought likely that the scrotal turgescence in the human new born is caused by the same factor. Due, however, to the generally homologous nature of the labia and the scrotum it is not possible definitely to assert that the active oestrogenic principle (theelin or oestrin) may not be involved.

The human female and probably the great apes are the only known forms in which this great concentration of gonadokinetic principles exists throughout pregnancy‡. On the male it has been shown experimentally that the testis increases greatly in size while in the inguinal canal, and that the interstitial cell mass is also increased many times above that of the control after treatment with pregnancy urine. The same type and degree of change seems to occur in the human foetus of the 8th to 9th lunar month, during the period when normally the descent into the scrotum is completed.

Of the animals known to the writer, it is only in the human in which the testes descend before or at birth. In others, in which the inguinal canal remains patent throughout life, testicular descent is associated with the first phases of puberty. In others the testes are elevated into the canal or the abdomen at the close of the breeding season, and are again found in the scrotum at the beginning of the next breeding season. This latter arrangement is therefore directly correlated with the pituitary-gonadal relationship.

In the human, however, the descent of the testis occurs at a time when the hormone production of the foetal pituitary, while active, must be of a low degree. But though the pituitary of the foetus is not markedly active, it is clear that the similar gonad activators are present in the blood of both mother and foetus, and the biological response of the foetal genital organs are in every way similar to that of experimental animals.

The theories regarding the descent of the testes are legion, and are for the most part purely mechanical. It is probable that the present interpretation on a basis of hormonal activation cannot disregard the mechanical factors. The importance of the gubernaculum testis has always been stressed in affording a directive and possibly a tractor influence. The

‡The mare has a certain amount of an active principle in the blood during the middle third of pregnancy; vide Cole and Hart, Am. J. Physiol. **93**: 57. 1929.

gubernaculum is present in these experimental monkeys, and it is seen that the portion of the thin fiber bundle which is attached to the scrotum may exert some traction on the testis which will tend to draw the testis down as the scrotum increases in size and moves farther away from the pubis and the perineal floor. Another mechanical factor is the two-fold increase in the size of the testis in the inguinal canal which itself undergoes no increase in size in so short a period. Since in both monkey and human the internal ring is normally closed shortly after the testis enters the canal, the growth of the testes would cause progress in the funnel-like canal and in this passive though hormonally controlled manner, move into the scrotum.

This concept of a hormonal action in causing the normal descent of the testes at birth in the human appears valid, but several points regarding undescended testes are not clear. John Hunter spoke of the retained testis as being "faulty and imperfect." In cases where neither testis leaves the abdominal cavity it is more probable that the testis did not react to the stimulus of the hormones of pregnancy than that the hormone level dropped at too early a period before the testis was sufficiently differentiated to respond. In the case of a single retained testis it is more probably a mechanical fault in the course of descent or of the canal itself.

Since the normal size of the testis is due to hormone action, and such stimulation is at least the inciting factor in the normal descent of the testes, the question could well be raised as to the validity of operative procedures in scrotal placement of an undescended prepubertal testis, except for cosmetic reasons.

Schapiro (1931) has already reported a reasonable degree of success in causing the descent of the testes in adolescent boys by the use of "Prähormon."

SUMMARY

Injections of extracts of pregnancy urine and water soluble extracts of anterior pituitary have been used in causing the descent of the testes in 10 immature Macacus monkeys.

The increase in size of the testis and the accompanying scrotal growth and turgescence are a result of hormone treatment, and seem to be important requisites in causing the descent.

The increase in the amount of the interstitial cell mass in the testis of the eighth and ninth foetal months are similar to the experimental increase in the amount of this tissue in monkey testes after injections of pregnancy urine.

The scrotal response in monkeys is similar to that obtaining in the human new born, which has the identical factors, derived from the maternal circulation or placenta, in its own blood as was injected into the experimental animals.

The human is the only organism known to the writer in which the testes descend at birth, and the human female is also the only one which is known to have this gonad-activating principle in the circulation throughout the period of gestation.

The conclusion appears logical that this hormone is involved in the natal descent of the testes in the human.

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STUDIES INDICATING THE FUNCTION OF CORTIN*†

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There are three lines of approach to the study of the function of *cortin* the vital hormone of the adrenal cortex; one, through the effects of deprivation, a second through the effects of replacement in deficient subjects, and the third through the action of cortin in normal subjects.

EFFECTS OF CORTIN IN DEFICIENCY

The most striking results occur when there is a deficiency of the hormone. In experimental adrenal insufficiency symptoms develop which indicate marked changes in the functions of many tissues of the body. Animals with both adrenals removed not only become fatigued easily when they undertake exercise, but they show a disinclination for exercise. Loss of appetite appears sooner or later, with or without vomiting, and there may be hemorrhages from the mucosa of the alimentary canal or elsewhere. As the animals become worse, they lose interest in their surroundings, finally passing into a state of inertia which verges upon coma or they become easily irritated and may appear irrational (wandering about aimlessly from one place to another without being satisfied anywhere), finally passing into coma, from which they are roused with difficulty. Just preceding or alternating with coma, twitching, heightened motor activity, and even convulsions sometimes occur. The blood urea rises and the blood sugar may fall. Although the changes seem to be coming on gradually, collapse may occur suddenly. In addition to the symptoms described for animals, in man other symptoms evident are pain in the legs, back or abdomen; insomnia and mental depression; poor judgment; failure of memory and lack of cooperation. With the administration of cortin the symptoms tend to disappear in the reverse order of their appearance; coma being replaced by heightened muscular irritability, as shown by increased motor activity, aimless movements, twitching and marked myotatic response to stimuli. As consciousness returns, the subject may be disoriented and become irritable, uncooperative and sometimes noisy. He shows evidence of drive, as indicated by this overactivity. The state of increased irritability gives way to one of calm; twitching and restlessness disappear. Pain is relieved and the patient becomes more rational and sleeps much. This is followed by the stage of recovery in which mental alertness returns; asthenia is decreased and appetite is restored. The patient sleeps well at night, is actively interested in his surroundings

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†Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 10, 1932.

and no longer sleeps much during the day. His insight and judgment are greatly improved and he becomes cooperative. In man the effects begin to appear within a few hours after the injection. In animals, where proportionally larger doses can be given, marked effects have been noted within an hour after injection in some instances, although it is usually a matter of hours with them also. The stage of recovery is reached within about three days after beginning treatment.

If cortin is discontinued in animals with complete adrenal insufficiency or in man with marked insufficiency, it is usually two or three days, sometimes longer, before the symptoms begin to reappear.

A somewhat more detailed consideration of the effect of cortin in adrenal insufficiency is necessary in order to indicate its functions.

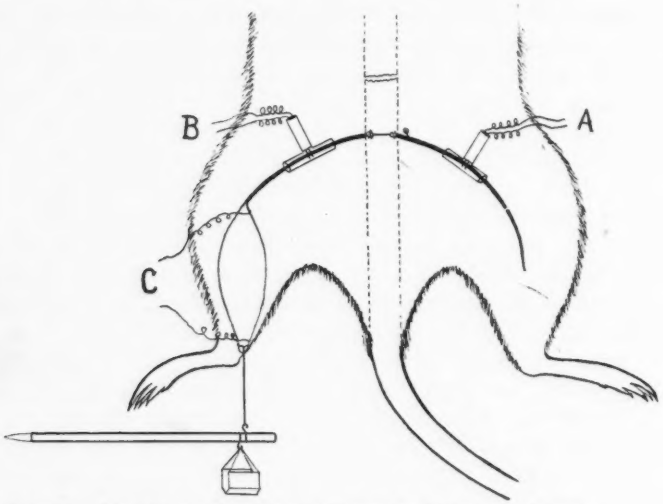

Figure 1. Diagram of reflex preparation showing location of electrodes.

Fatigue. The symptom of fatigue is one of the earliest to appear in insufficiency and among the last to disappear under treatment. We have been able to show that this symptom involves the reflex, as well as the myoneural junction and the muscle itself.

Both adrenals were removed from young rats. These were divided into two groups (16 cortin and 11 sodium chloride treated), the first receiving cortical extract twice daily and the second an equal volume of isotonic sodium chloride solution for control. After a week or ten days the animals were anesthetized with amytal; the spinal cord was cut just below the level of the diaphragm and the tendon of the left gastrocnemius was cut and attached to a scale pan after-loaded with a 100 gm. weight (Fig. 1). The electrodes were arranged for stimulation of the muscle directly, through its nerve and by way of the reflex through stimulation

of the opposite sciatic nerve, which was cut peripherally. For stimulation, a spring was used to make and break the primary circuit of an inductorium about three times a second. Both make and break shocks of the secondary coil were used. The stimulus was supramaximal. The reflex was fatigued, immediately after which the stimulation was switched to the nerve that supplied the muscle. As soon as fatigue was developed through this path the muscle was stimulated directly. A comparison of the resistance to fatigue has shown that the cortin treated animals are much more resistant than those injected with sodium chloride. Although the cortin-treated animals fall short of having the resistance of normals, nevertheless, the difference between the two sets is significant (Fig. 2). There is evidence that more frequent injections of cortin will increase the difference between the two series.

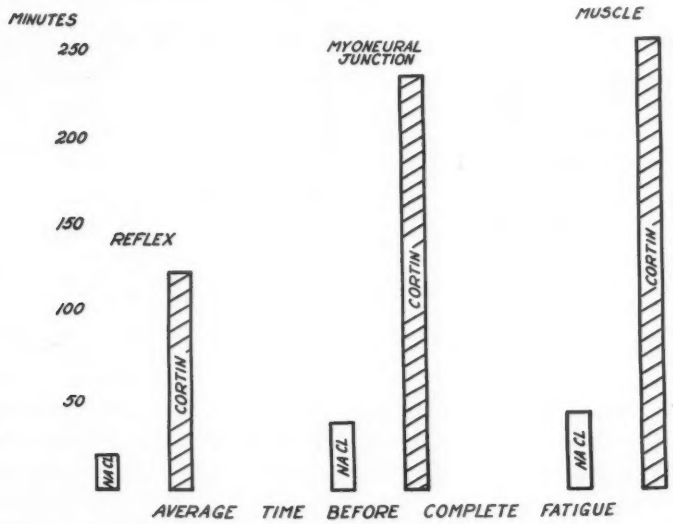

Figure 2. Effect of cortin on resistance to fatigue in adrenalectomized rats. Average of 16 cortin treated and 11 sodium chloride treated rats.

Gans and Miley (1) showed that the nerve muscle preparation in adrenalectomized rats was fatigued in a much shorter time than was that in a normal animal. However, they did not further localize the seat of fatigue. If one gives cortin in cases of Addison's disease, he will observe that among the symptoms to be affected are those involving the nervous system. The effects on these symptoms are as striking as on any other part of the syndrome. Indeed, it has been shown by Hartman, Beck and Thorn (2) that cortin has an effect on the nervous manifestations of certain other clinical conditions unrelated to Addison's disease. Mental fatigue may be diminished, a sense of well-being even to the point of euphoria may develop and sleep may be improved, if faulty. In normal

human subjects, similar results are obtained, and are more pronounced if the individuals are tired, depressed, or sleep poorly. These observations indicate that cortin influences the nervous system generally, as well as the muscular system, and that this influence is fully as marked as that on any other system of the body.

Resistance to Cold. Adrenalectomized animals and patients with adrenal insufficiency (Addison's disease) have a lowered resistance to cold. Indeed, cold can be used to accelerate the development of adrenal insufficiency. We have been able to show that this is due, in a large measure, to the inability of the animals to produce the extra heat required. At first adrenalectomized sodium chloride treated animals maintain their heat production fairly well, but after a few hours, this fails and may fall far below that maintained at room temperature (Fig. 3). Cortin treated

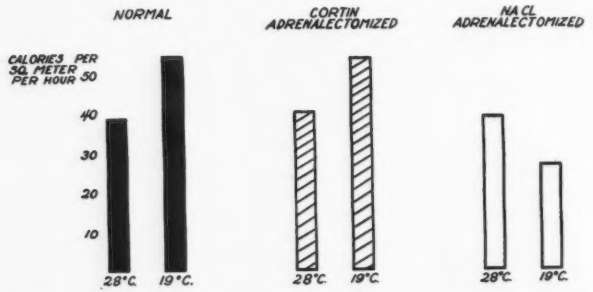

Figure 3. Heat production during the last four hours of seven hours exposure to cold. Average of three rats in each group.

adrenalectomized animals keep pace with increased heat production fairly well, even in the later hours. It was thought that this failure to produce heat in adrenal insufficiency after exposure to cold was due to a reduction in the blood sugar which tends to be low, especially in the late stages. A comparison of the sugar values with the temperatures of albino rats, as shown in the accompanying table (Table I), demonstrates conclusively that low blood sugars are not responsible for the low resistance to cold; as high values may be found in animals with low temperatures—those who will die—and low values are to be found in animals who resist the cold very well. If one averages the blood sugar values in all of the rats having temperatures above 30° C. at the end of the experiment—those who will survive—and compare this with the average from the animals having low temperatures—many of which will die—he obtains 75.9 mgm. per 100 cc. and 74.4 mgm. per 100 cc. respectively—an insignificant difference. In view of the easy fatigue of the reflexes after adrenalectomy the failure to produce the extra heat might be explained on this ground. Much of the heat production comes from muscular activity. As the reflexes become fatigued this activity would fail.

TABLE I

BLOOD SUGARS AND TEMPERATURES OF RATS AFTER EXPOSURE TO 9°C. FOR 4.7 HOURS

Rat	T. C.	Blood Sugar mgm. per 100 cc.
Normal		
1	38.0	122 (struggled)
2	38.2	106
3	38.0	101
4	37.0	99
Adrenalectomized		
1	37.3	84
2	37.0	63
3	36.0	57
4	35.8	93
5	35.3	75 (struggled)
6	35.0	104 (struggled)
7	35.0	68
8	34.0	83
9	32.6	75
10	32.3	50
11	31.7	104
12	31.4	65
13	30.5	93
14	30.3	68
15	30.2	57 (struggled)
16	30.0	54
17	30.0	68 (struggled)
18	27.0	74
19	26.7	79
20	26.0	130
21	25.2	63
23	25.0	106
24	24.6	93
25	24.2	72
26	23.0	36
27	23.0	43

Resistance to Heat. Adrenalectomized rats show a lowered resistance to heat. When these, together with normal animals, are exposed to a temperature of 37-40°C. at first all are restless. A little later, however, the adrenalectomized animals become quiet and try to sleep, only occasionally moving about. Still later, varying from one to two hours, they become prostrate, while the normal rats only show discomfort by continually moving about the cage and washing themselves with saliva. The adrenalectomized animals easily pass into convulsions, which can be brought on by a slight stimulus. Frequently these die at a temperature which is not serious for the normals. Cortical extract can protect adrenalectomized animals to a considerable degree. If cortin injected and sodium chloride injected rats are placed in the same high temperature, the difference between the two is much like that between normal animals and untreated adrenalectomized animals, except that it is not quite so striking.

A study of the water content of some of the tissues of the body indicates that there is a reduction in the shift of water from the reservoirs. This would hinder heat loss (Fig. 4). It will be noted that the water content of the blood and muscle does not differ greatly when one compares normal with adrenalectomized animals. In the liver and skin, however, there is an appreciable difference. In the latter, the water content in the

cortin treated adrenalectomized animals lies midway between that of the sodium chloride treated adrenalectomized and the normal rats. We have also noted that heat exacerbates the symptoms of adrenal insufficiency in cats. To illustrate: One cat, with both adrenals removed, was not injected with cortin until in a state of collapse several days after the operation. The administration of cortin in a few hours enabled this cat to stand and to show decided improvement. We placed the animal near an electric heater, which was certainly not too warm for a normal animal yet, a few minutes later, the animal was again in a state of collapse, from which it was impossible to revive him by frequent injections of cortin. Some patients with Addison's disease state that they do not feel so well in hot weather. Moreover, they are much more easily fatigued at temperatures which are without effect on normal individuals.

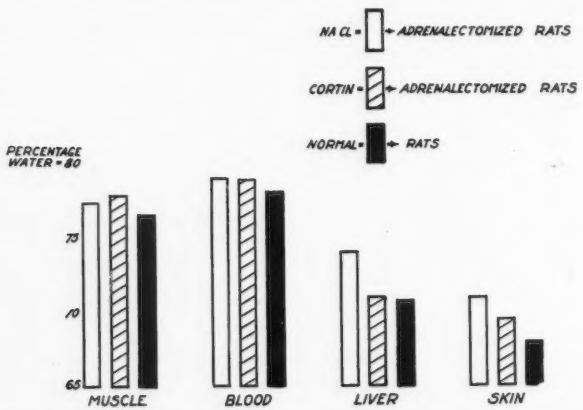

Figure 4. Water content of tissues in normal and adrenalectomized rats after exposure to a temperature of 37°C. Average of 10 normals, 14 adrenalectomized cortin treated and 14 adrenalectomized sodium chloride treated rats.

RELATION TO GONADAL FUNCTION

In Addison's disease menstruation may cease, to return with treatment by cortin. In normal women it has been possible to shorten the interval between the menstrual periods from three to five days. This has been demonstrated in four subjects. A fifth subject showed no reduction in the interval, but pain began one week before and continued during the period. This had rarely been experienced before. In Addison's disease (2), libido, which had diminished or disappeared in both male and female, returned to normal after treatment with cortin.

It has been shown by Wyman (3) that oestrus may be partially or completely inhibited in adrenal insufficiency. Connor (4) found that a sufficient dosage of cortical extract produced inhibition of oestrus in normal white rats. We have been able to confirm Connor's findings. Corey and Britton (5) state that extracts of the adrenal cortex produce preco-

cious sexual maturity in the albino rat, the effect being most pronounced in the female. Atwell (6) found that in hypophysectomized tadpoles treated with cortin the ovaries were two and one-half times as large as those of untreated controls. It would seem, therefore, that cortin is necessary for gonadal function.

RELATION TO METABOLISM

Adrenalectomized animals, especially rats that have not reached their full growth, show a lower metabolism than normal. It may drop 10 to 20 per cent where it remains for a time only to fall again just before death. The first reduction in metabolism may occur within two days after adrenalectomy. However, it is possible to maintain metabolism at the normal level or bring it back to normal by the injection of cortin after it has fallen due to cortical insufficiency. In 1928, (7) we showed that metabolism of adrenalectomized cats could be maintained within the normal limits with very small amounts of cortin. Swingle, Pfiffner and Webster (8) in 1931 confirmed our results and carried the work further in that they demonstrated that adrenalectomized cats allowed to pass into the late stages of adrenal insufficiency could be brought back to normal by cortin.

RELATION TO GROWTH

The cortical hormone is essential to growth. This was indicated in the growth curve of adrenalectomized rats (9). It is also shown by the slow healing of wounds after adrenalectomy. This may be increased and approach normal if an adequate amount of cortin is injected. Moreover, injuries create a greater demand for cortin, for we have found that more extract must be given after extensive injuries than after those of a minor character.

RELATION TO TOXIN RESISTANCE

It has recently been shown by Perla and Marmorston-Gottesman (10) and Hartman and Scott (11) working independently that cortin increases the resistance of adrenalectomized animals to certain bacterial toxins (typhoid vaccine and dead Staphylococcus). Toxins increase the demand for cortin. Adrenalectomized animals contracting infections must be injected with considerable amounts of extract in order to recover. Likewise in Addison's disease the cases which are being maintained at a constant level with a certain dosage require much more extract if infections are contracted and sometimes succumb to a minor infection.

RELATION TO KIDNEY FUNCTION

Marshall and Davis (12) demonstrated that the kidney of adrenalectomized animals has a reduced function. The non-protein nitrogen is raised in the blood and lowered in the urine. We have demonstrated that cortical extract lowers the high non-protein nitrogen in the blood in both adrenal insufficiency of animals and in Addison's disease. Cortical extract also increases the water intake and urinary output. In late stages of cortical

insufficiency in both man and animals the water intake is much reduced and may go so far as to cause dehydration. Following the injection of cortin the intake of fluids soon establishes the water balance; urinary output returns to normal and may even indicate diuresis for a time possibly due to the waste substances that have accumulated in the blood.

RELATION TO BLOOD SUGAR

The low blood sugar frequently encountered in the late stage of adrenal insufficiency can be raised to normal by the administration of an adequate amount of cortin.

CONCLUSION

We have shown that cortin is intimately related to the functions of muscle, nervous tissue, kidney, and gonads. Perhaps when other tissues are investigated they will be found to be just as directly concerned. It is difficult to explain these effects through the primary action on any one function of the body. Cortin, therefore, seems to be necessary for the activity of the various tissues of the body. We suggest that it may be a general tissue hormone.

SUMMMARY

1. The effect of cortin upon the symptoms of adrenal insufficiency in man and animals, is described.

2. Proof that cortin affects the nervous system as well as the muscular system is given.

3. The early fatigue of the reflexes is offered as a partial explanation of the reduced heat production of cortin deficient animals upon exposure to cold. Low blood sugar levels are not responsible.

4. The lowered resistance to heat in cortin deficient animals may be partly due to reduction in the shift of water from the reservoirs.

5. Cortical extract shortens the interval between menstrual periods in normal women. This extract when injected in sufficient amount inhibits oestrus in normal white rats.

6. The effects of cortin on metabolism, growth, toxin resistance and kidney function are described.

7. It is suggested that cortin is a general tissue hormone.

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PUBERTAS PRAECOX IN A GIRL OF FOUR

AN ATTEMPT TO ESTIMATE THE FOLLICULAR AND ANTERIOR PITUITARY SEX HORMONES*

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LOS ANGELES

Pubertas praecox in the female is characterized by early menstruation accompanied by the anatomical and functional changes of maturity and emotional attraction to the other sex. All of these diagnostic criteria are well on the way to full development in the case here reported. Others have given historical resumes of the few cases reported. I will confine myself to consideration of the present case in which, in addition to the ordinary symptoms, we demostrated the mature proportion of estrin in the blood.

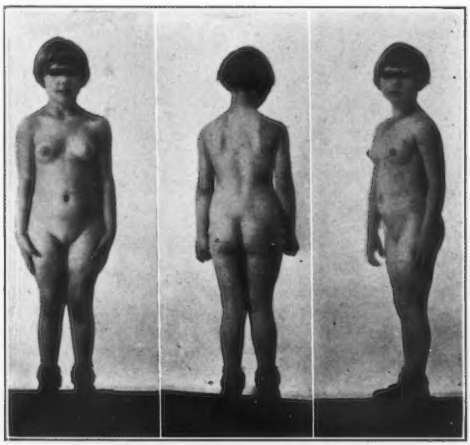

Figure 1. Pubertas praecox in a girl aged four years. Note breast and hip development.

L. Y., 4 years old, was brought in because she suffered from painful breasts toward the end of each menstrual cycle. She presented the appearance of a precociously developed girl of eight years, with breasts as well formed as those of the ordinary girl of fourteen. The breasts on palpation appeared to have an adult proportion of secreting tissue. The mother was a slight woman who herself had begun to menstruate at ten years. Another daughter had been born two years following the birth of the girl we studied. This sister and a brother seven months old were normal.

At the age of four months L. Y. had the first showing of blood from the vagina. The discharge was light in color and lasted about twelve hours. Four weeks later she had a flow lasting two days which was like an ordinary menstruation. The next month the flow lasted three days and menstruation has been regular ever since at twenty-eight day intervals and lasting three to four days. There were no clots and the odor was normal.

*Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 9, 1932.

Physical examination showed a girl quite active and strong, plump, with well developed hips and very prominent breasts. Her height was 46 inches and weight 53 pounds.

She weighed eight pounds at birth, her first teeth erupted at four months, she began to walk at one year but did not talk until the age of three years when she began with ordinary conversation. She talks like an adult and is strongly attracted to men. She crawls all over men when given the chance. She has never had a serious illness.

The breast development was noticed at one year and shortly after, it was noticed that the breasts became tender and swollen the week before menstruation. Her growth was rapid from the first. She has no childish craving for sweets, she drinks six or seven glasses of water a day. She is very active in play, but has spells of sudden fatigue. About once a day she suddenly ceases her activities, lies down, goes to sleep immediately. After two hours sound sleep, she awakes refreshed and as active as ever. Mentally she is classified as dull normal and slow.

A blood count showed 5,370,000 red cells; haemoglobin, 85 per cent; white cells, 12,200; polymorphonuclears, 45 per cent; lymphocytes, 51 per cent; transitionals, 3 per cent, eosinophiles, 1 per cent. The Wassermann reaction was negative; the bleeding time, three minutes; the blood calcium, 10.5 mgm. per cent.

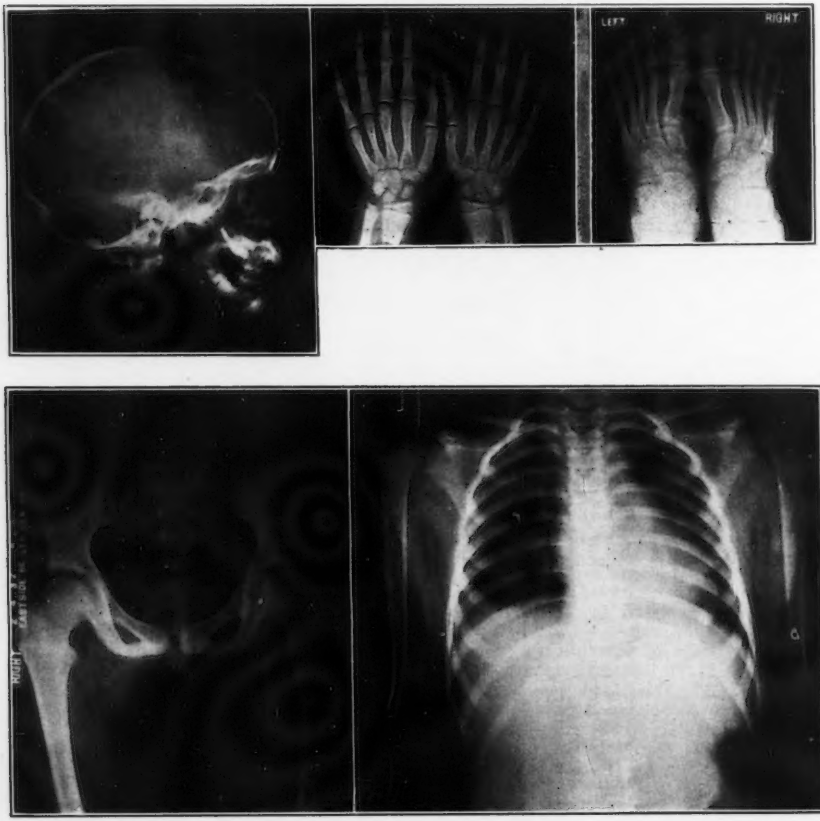

Figure 2. Roentgenograms of girl in Figure. 1. Skull shows normal sella. Wrists show eight carpal bones. Foot bones are well developed. Hips and pelvis show advanced development and the arms and shoulders advanced ossification.

Skiagrams showed marked premature ossification and epiphyseal fusion with general growth beyond her age. All the eight carpal bones were ossified. The pisiform, which does not usually appear until after eight years, was well developed in both wrists and had probably been there for some time. The pelvis showed both greater and lesser trochanters present and the os pubis and ischium had united. The skull was well formed and larger than normal for her age. The sella was large but proportionate to the rest of the skull. The mastoids were well developed.

The pelvic measurements were: interspinal, 17.5 cm.; external diagonal, 13.5 cm.; intercrestal, 19 cm.; intertrochanteric, 23 cm.

Pelvic examination was made through the rectum by Dr. Kavinoky. She reports the uterus about the size of that of a ten year old, straight up the abdomen, without anteflexion or angulation between the cervix and fundus. No mass suggestive of tumor was palpable. The ovaries were not palpable. The vulva had about the appearance of that of a ten year old girl and there was slight pubic hirsutes. The clitoris was not large. There was no excess hair on any part of the body. The skin was normal.

Dr. Leo T. Samuels of the College of Medical Evangelists Research Laboratory made a study of the ovarian follicular hormone and the pituitary hormone in this case and reported as follows:

"Forty cc. of blood was taken one week before the haemorrhagic phase of the menstrual cycle. The follicular hormone test was carried out by a modification of the Frank test with the animals carefully controlled. Thirty cc. of venous blood was extracted with ether and the latter removed by evaporation. The residue was dissolved in 0.2 cc. of hot ethyl alcohol and 2 cc. of isotonic sodium chloride added. This gave a fine uniform suspension. The suspension was injected into an ovarectomized mouse in three doses during one day and the vaginal smear followed three times a day during the succeeding four days. The extent to which leucocytes were replaced by squamous epithelial cells was used as a measure of the follicular activity. The mouse used had been previously injected with crystalline theelin. One mouse unit of theelin gave a reaction containing largely nucleated epithelium—a '3' reaction. One and a half mouse units gave large amounts of non-nucleated epthelium—a '2' reaction. With the blood suspension the highest point reached was a '2' reaction, this was a definite effect equivalent to that which is obtained about seven days before the menstrual haemorrhage with forty cc. of blood from a mature woman.

"The pituitary test was made by the Fluhmann technique. Blood serum was injected into immature female mice nineteen days old, in seven doses of one-half cc. each, two injections per day. No precocious maturity was evident. This negative result is the one usually found in normal women.

"One sample of urine was also examined. This sample was extracted in a continuous extractor with butyl alcohol, the alcohol distilled off, the residue dissolved in petroleum ether, and the latter shaken with three portions of half normal sodium hydroxide solution. This solution was then neutralized with HCl and the resulting saline solution made up to definite volume. Aliquot portions were injected in divided doses into standardized mice (standardized according to the method given under the blood test). The sample of urine contained 5-7 mouse units of follicular hormone.

"Evidently the ovaries of this girl are definitely functioning as sources of follicular hormone, probably due to pituitary stimulation. The latter, however, is no higher than in normal mature women. How much lower the pituitary concentration might be, we cannot tell with our present methods of determination."

Within half an hour after five units of pituitrin, the patient paled markedly, began to complain of pain in the abdomen, and had a bowel movement. She drinks relatively large amounts of water daily. We were unable to get a water balance observation because the family became non-cooperative after so many tests. We had intended to continue weekly blood hormone tests through a complete menstrual cycle. This also was denied us.

SUMMMARY

The case is reported of a girl who first showed a bloody vaginal discharge at the age of four months. Twenty-eight days later she had a menstrual discharge lasting two days. Since then she has had regular menstrual periods at 28-day intervals, with a hemorrhagic phase lasting three

or four days. She grew rather rapidly, and at the age of four years was the size of a girl of six years old, with the breast and hip development of a well-developed 14-year-old. The breasts showed marked development at the end of the first year, and from that time on became large and tender the week before menstruation. Her osseous development was advanced from three to seven years. Assay of the blood showed the presence of estrin in the normal proportion usually found in the adult normally menstruating woman for the period of observation, one week before menstruation. Mentally, she is classified as dull normal. She is markedly attracted to men. Her ovaries were not palpable, and no pelvic, abdominal or intracranial new growth could be demonstrated.

NOTE.—Re-examination of this girl early in September and six months after the data compiled above reveals the left ovary palpable and the size of a small hen's egg. This is probably an ovarian cyst.

TREATMENT OF THE ANEMIA OF MYXOEDEMA*

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Anemia of a mild or moderate degree is a common occurrence in myxoedema and has received extensive comment in the literature. Stone (1), and Emery (2), to mention only two of the workers in this field, are of this opinion. On the other hand, Mackenzie (3), reporting three cases of anemia in hypothyroidism, states that anemia is not a prominent feature in the great majority of cases. Most writers note that the anemia improves in some cases as the myxoedema is treated. On the experimental side, several investigators have found that thyroidectomy in animals produces an anemia which responds to thyroid feeding. Kunde (4) et al. have recently shown that the anemia of hypothyroidism in rabbits is characterized by a greater than normal diameter of the erythrocytes and a color index greater than 1, and that thyroid feeding causes a reticulocyte response varying from 4 to 10 per cent, together with the disappearance of the anemia. Hoskins and Sleeper (5) have reviewed some of the literature on this subject. They show that thyroid feeding in non-myxoedematous subjects has an effect on the blood. In 13 out of 15 patients with dementia praecox there was a rise in the number of red blood cells after a prolonged period of thyroid administration. On the other hand, Deusch (6) is of the opinion that there is no relationship between the thyroid and the hematopoietic system, and that in neither primary nor secondary anemias has any response been obtained by the use of thyroid.

Recently we have attempted to accelerate the regeneration of blood in these anemias or to initiate it in those cases not improved by thyroid. The medications tried consist of liver (whole liver or liver extract), iron, and liver plus iron. The red blood count and hemoglobin content were followed at frequent intervals and in some, the reticulocytes as well. The attempt was made to evaluate in some instances the relative importance of each one of the agents used in the treatment of the different types of anemia accompanying myxoedema. The following cases are presented to illustrate some of the results.

Case 1 (Figure 1.) This patient had a level of metabolism of minus 36 per cent, a red count of 3.5 million cells† and hemoglobin (S)‡ of 55-60 per cent. There was no free acid in the gastric juice. In the course of nine months

*Read before the Sixteenth Annual Meeting of the Association for the Study of Internal Secretions, New Orleans, May 10, 1932.

†It is to be noted that very often the red blood cell count and hemoglobin content are reduced soon after the beginning of thyroid medication. This is probably due to dilution of the blood concomitant with the increase in plasma volume induced by thyroid in myxoedema which was demonstrated by Thompson (7).

‡S—Sahli.

of thyroid medication, the red count rose to about 5.3 million cells and the hemoglobin to about 80 per cent (S). This level of blood has been maintained to date.

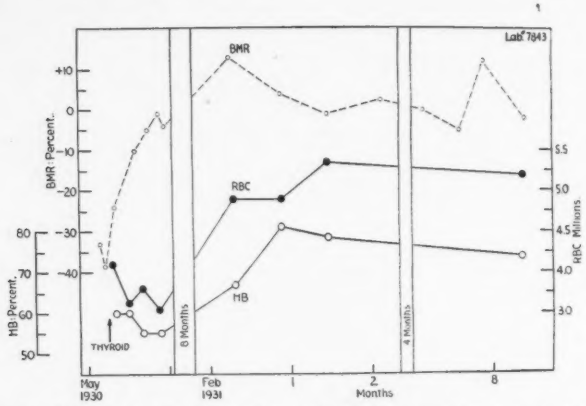

Figure 1. Changes in the blood of a patient with secondary anemia and myxoedema under the influence of thyroid medication only.

Case 2 (Figure 2). The initial drop in red count and hemoglobin after the beginning of thyroid medication was followed by the introduction of 100 grams of liver and 4 grams of iron or less, in the form of iron and ammonium citrate crystals, daily. The time interval for these treatments, as indicated on the chart, was 50 days and 30 days respectively. There was practically no change during the time of actual treatment, but in the period of 12 days after omission of liver, the red count rose from 3.7 million to 4.7 million. The time relation of this rise to the therapy used and the rapidity of response suggest that the medication played some role. It is difficult to say which was responsible, iron or liver, or both. The data would favor the liver as the important factor. There was an additional but slower increase in the red count to over 5.0 million cells in the course of 8 months. The hemoglobin, which failed to respond to the combined use of liver and iron, also increased about 10 per cent in the course of the latter period. The failure of the hemoglobin to respond may have been due to inadequate dosage, particularly of iron. There is some ground for this sur-

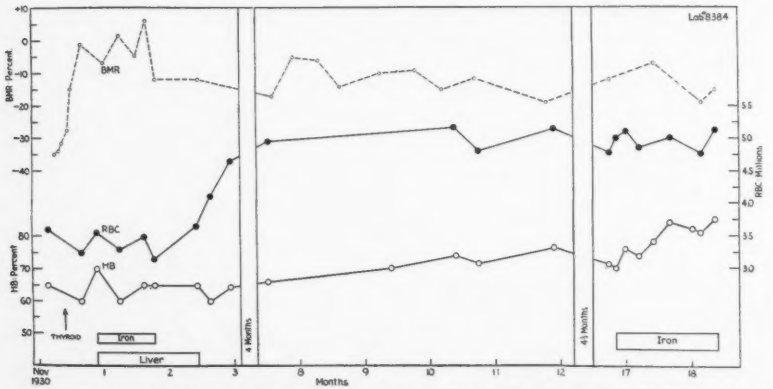

Figure 2. The response of the red blood cell count and hemoglobin content to thyroid and liver (100 grams daily) plus a small dose of iron (4 grams or less of iron and ammonium citrate daily). A larger dose of iron (8 grams daily) was used after a lapse of about 14 months.

mise in that a larger dose of iron (8 grams daily), subsequently used, caused a rise of about 15 per cent in hemoglobin content in the course of six weeks.

Case 3 (Figure 3). This patient has received thyroid extract from May, 1924, to date except for a short period of omission for two months in the

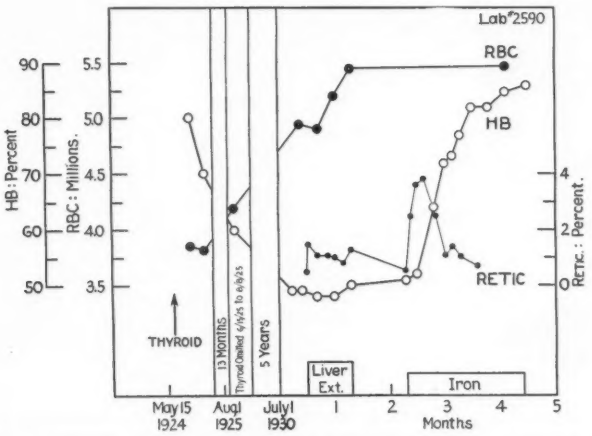

Figure 3. Changes in the blood caused by liver extract (4 vials daily) and iron (4-8 grams daily), administered separately, in a case of long standing anemia with a normal red count and low color index.

summer of 1925. By July, 1930, the red count had risen to five million from an initial level of 3.8 million cells, but the hemoglobin had dropped from 70 (T)* to 49 per cent (S). Liver extract (Lilly 343) 4 vials daily by mouth was given for a period of a month. The net result was a rise of about half a million cells in the red count. There was no reticulocyte response and the hemoglobin remained unchanged. A month after the omission of liver extract, iron, in the form of iron and ammonium citrate, was administered in the dose of 4 to 8 grams daily for two months. There was a reticulocyte response to 3.8 per cent on the ninth day, followed by a prompt rise in the hemoglobin content to 80-85 per cent (S). The red blood cell count was not affected.

Case 4 (Figure 4). This patient with a secondary anemia and anacidity showed very little change in the blood picture after thyroid medication for a month. Liver extract (Lilly 343) 3 vials daily by mouth was then substituted, but nothing happened to the blood. After 15 days, iron and ammonium citrate 8 grams daily by mouth was added and the liver extract continued. There was also no reticulocyte rise but the blood slowly rose to normal in about two months. The liver extract was given for one month only and whole liver, half a pound three times a week, was substituted. In spite of the prolonged treatment with iron and liver, the blood changed very little. It seems that in this case medication improved the blood picture more rapidly than would have taken place on thyroid alone, if at all.

Case 5 (Figure 5). In this case there was, at the beginning, a moderate secondary anemia and no free acid in the gastric juice. After 18 days of thyroid medication, the red count remained the same and the hemoglobin dropped slightly. Liver extract, 2 cc. intramuscularly daily for 13 days, caused a reticulocyte rise from 0.2-0.3 per cent to 2.0 per cent on the fifth day followed by a slight rise in the red count. The hemoglobin changed very little. Iron and ammonium citrate 8 grams daily was substituted. The reticulocytes, unfortunately, were not determined, but the red cells slowly increased by a million in about two months and an additional three-fourths of a million in the third

*Tallquist.

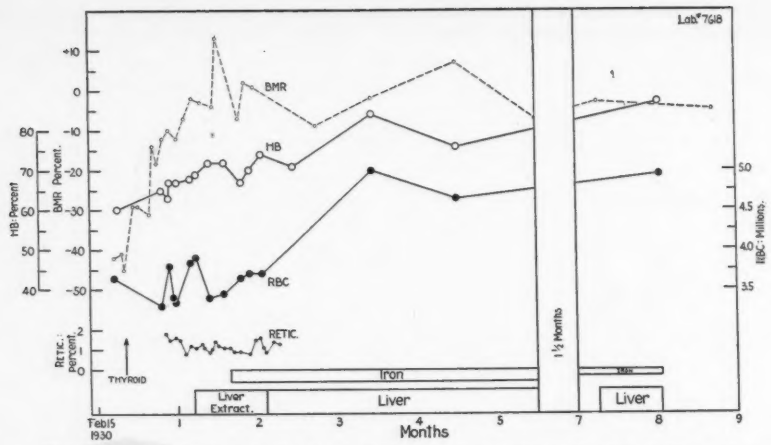

Figure 4. The effect upon the blood of thyroid, liver extract (3 vials daily), and iron (8 grams daily) plus liver extract (or liver, half a pound three times weekly) administered in succession.

month. It is possible that part of the first rise in the red count was due to the effect of liver extract rather than iron. The hemoglobin rose very little (less than 10 per cent) in the first two months of iron therapy, but in the third month rose rapidly to 75-80 per cent (S). After five months of iron medication, whole liver, 200 grams daily, was substituted. This caused very little change, but since the blood picture was nearly normal, marked changes could not be expected. After a period of three and a half months, iron, in the same dose as before, was added in order to determine if the combined use of iron and liver would improve the blood any further. This caused an additional rise of about 10 per cent in the hemoglobin in the course of two months. The initial improvement in the blood may properly be considered as due to the accelerating effect of iron and possibly liver extract on blood regeneration, whereas the latter part of the improvement was probably due to the iron and liver entirely.

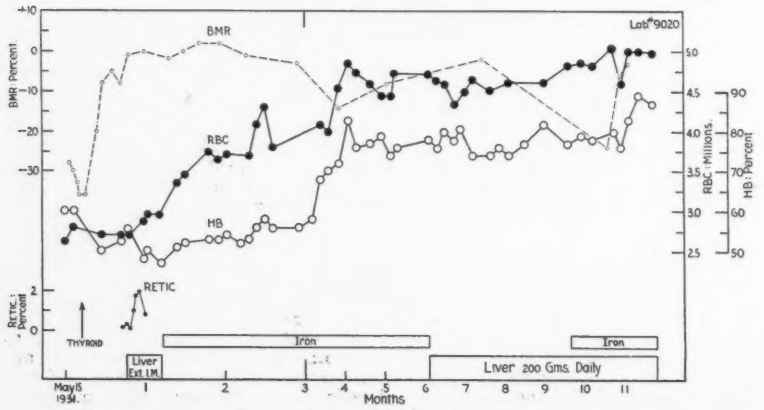

Figure 5. The effect upon the blood of thyroid, liver extract (2 cc. intramuscularly daily), iron (8 grams daily), whole liver (200 grams daily), and liver plus iron, administered in succession.

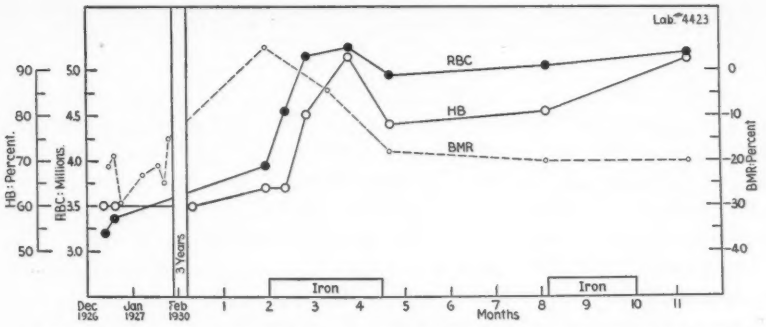

Figure 6. Changes in the blood due to iron (6 grams daily) in a case of long standing secondary anemia not improved by thyroid.

Case 6 (Figure 6). The anemia in this case persisted in spite of adequate thyroid therapy for three years. On iron and ammonium citrate 6 grams daily, there was rapid improvement in the red blood cell count and hemoglobin content. There was a parallel clinical improvement. As indicated in the chart, three and a half months after the omission of iron, a slight rise in hemoglobin from 81 per cent to 93 per cent was obtained by a second course of iron therapy.

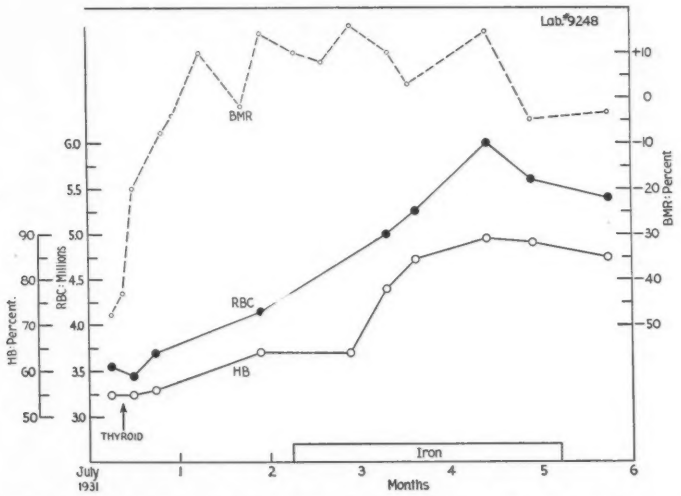

Figure 7. The accelerating effect of iron (8 grams daily) in a case of secondary anemia responding partly to thyroid.

Case 7 (Figure 7). This patient had a moderate anemia with a red count of about 3.5 million cells and hemoglobin of 55 per cent (T). Also the maximum free acidity of the gastric juice after stimulation with histamine was 16 cc. of 0.1 normal acid. On thyroid medication for a month and a half, the red blood cell count rose to 4.2 million and the hemoglobin to 64 per cent (S). One cannot be sure of the rise in hemoglobin because of the two different methods used in its determination. Following the administration of iron and ammonium citrate, 8 grams daily, there was a fairly rapid increase in red count to around 5.5 million cells and hemoglobin to 90 per cent (S). In this case there probably would have taken place a rise in red count under thyroid medication alone. It

seems that iron merely accelerated this rise. In the case of the hemoglobin, however, iron probably supplied the major, if not the entire stimulus for the response.

DISCUSSION

It is our belief that anemia is a common finding in patients with myxoedema. Of the 52 patients studied in this clinic in the past six years 60 per cent had red blood counts below 4.0 million cells and 52 per cent had hemoglobin values below 70 per cent (T). In another paper (8) we have shown that gastric anacidity is present in 53 per cent of the patients with myxoedema and that anemia is much more common in those with anacidity than in those showing free acid in the gastric juice. The anemia may be of the pernicious or the secondary type.

In a previous paper, Means, Lerman and Castle (9) reported five patients showing both myxoedema and pernicious anemia, each condition responding to the proper specific agent, thyroid and liver extract respectively. The relationship existing between these two diseases is difficult to recognize. It is conceivable that the loss of the sustaining action of thyroxin on the activity of the bone marrow may in some instances lead to the development of the pernicious type of anemia particularly in those patients showing gastric anacidity. The finding by Kunde et al. (4), already referred to, of a pernicious anemia like blood picture in hypothyroid rabbits lends some support to this conception. On the other hand, in some instances pernicious anemia antedated the myxoedema and in one case pernicious anemia developed in spite of thyroid medication for seven years.

The secondary anemia of myxoedema may fall into one of three groups: (1) The red blood cells and hemoglobin are proportionately reduced, giving a color index of 1; (2) the hemoglobin is reduced much more than the red blood cells, resulting in a color index of less than 1; (3) the hemoglobin only is reduced below normal limits, giving a color index of less than 1 also. It is our experience that some cases of secondary anemia will slowly return to normal under thyroid medication only (Case 1). The time necessary for this result is usually six months or longer. However, this response does not always take place with prolonged thyroid medication. The red blood count may slowly return to normal but the hemoglobin remain low or decrease as in Case 3, or both may remain unchanged as in Case 6. In Case 4, after a month and a half, in Case 5, after a month, and in Case 7, after two months of thyroid medication, the changes in the blood were slight or insignificant. This, in spite of the fact that in Cases 5 and 7, liver extract was used during part of the intervals mentioned. This possibility was suggested by Putnam (10) in 1893, when he raised the question whether the cause of anemia may not sometimes persist after the most striking myxoedematous conditions have passed away.

The role of liver and iron in the treatment of the secondary anemias of myxoedema is twofold: first, to accelerate the regeneration of the blood

that takes place in some cases under the influence of thyroid, and second, to initiate the changes in the blood in those cases in which thyroid is ineffective. Liver extract, given over a short period of time, fails to accomplish this (Cases 3, 4 and 5). At best, it causes a slight rise in the total red blood count (Cases 3 and 5), but very little reticulocyte response, if any, and little change in the hemoglobin content. In all probability liver will accomplish the same thing, as illustrated by Case 2. In this case, the inadequate dose of iron over a short period of time probably contributed little to the rise in the red blood count. The large increase in red cells in Case 2 is to be contrasted to the slight increase in Case 5 and no increase in Case 4 on liver extract, in spite of the fact that the levels of red count were the same or lower in these two cases. It is possible that the iron content of the liver is the important factor.

On the other hand, iron, in a form easily assimilated, and in adequate dosage, will initiate the return of the blood to normal (Cases 3 and 6), as well as accelerate the slow response following thyroid medication (Cases 5 and 7). It causes a response in the anemias in which both the red blood count and hemoglobin content are reduced (Cases 5, 6 and 7), as well as in those in which only the hemoglobin is reduced (Case 3). Iron is as effective in these cases as in the hypochromic anemias treated by Mettier and Minot (11), Dameshek (12), and Mills (13).

The combined effect of liver and iron seems to be no greater than that due to iron alone (Case 4). Liver, as an adjunct to iron, may be of value in the occasional case where the response to iron is not complete. It may permit the latter, and the most difficult part of the blood response to take place, as in Case 5.

SUMMARY AND CONCLUSIONS

Seven cases are reported that are illustrative of experiences that have led to the following conclusions:

Anemia in myxoedema is a frequent occurrence, and very often associated with gastric anacidity. In some cases the hematopoietic effect of thyroid is sufficient to cause the anemia to disappear slowly; in others the anemia persists or only the red blood cells return to normal.

Liver extract, or whole liver, accelerates or initiates regeneration of the red blood cells to some extent, but has little or no effect on the hemoglobin.

Iron, in adequate dosage, causes rapid improvement in anemia of myxoedema even in those patients who fail to improve on thyroid.

Liver, plus iron, is probably no more effective than iron alone, although this combination may be of value in obtaining the last part of the improvement in the blood.

In the practical management of myxoedema, therefore, iron should be given in addition to thyroid when a condition of hypochromia persists,

and liver extract should be given in those cases of myxoedema presenting the blood picture of pernicious anemia.

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EXPERIMENTS ON ENDOMETRIAL HYPERPLASIA*†

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The pathological entity now known as endometrial hyperplasia has been recognized for some time. It was not until after the work of Hitschmann and Adler that it could be interpreted as a non-inflammatory condition. Previous to the work of these investigators it had been generally considered to be a form of hypertrophic endometritis. The noteworthy exception to this statement is the view which was expressed by Cullen in 1900. He described this condition in his book on cancer of the uterus (3) as "endometrial hyperplasia." The condition is extremely common and is met with most frequently at the time of the menopause, although it can occur at any age. On account of its frequency, and tendency to recur, it has inspired a voluminous literature.

Recent advances in the field of the internal secretions have attracted the interest of almost all gynecologists, and many have hoped that these advances would explain the nature and etiology of endometrial hyperplasia. Schroeder (12) was the first to recognize the condition as being due to a disturbance of the ovaries. He found that cystic follicles were usually present but that there were no corpora lutea. His views have been confirmed in many recent contributions, notably by Wilfred Shaw (13), Novak and Martzloff (11), Graves (7) and others, and the condition is now universally recognized as being the result of an endocrine disorder.

As a result of the work of Smith and Engle (14) and of Zondek and Aschheim (15), on the relation of the hypophysis to the ovary, attention was focused on the anterior lobe as a possible cause of this hyperplasia. Hofbauer (9) (10) was able to produce changes of an undoubted hyperplastic nature in the uteri of guinea pigs by subjecting them to anterior lobe transplants and to injections of anterior lobe extracts. From this work he concluded that hyperplasia may reasonably be considered as a manifestation of an over-activity of the anterior lobe of the hypophysis. Frankl (6), in a paper devoted entirely to the discussion of Hofbauer's work, accepts over-activity of the anterior lobe as an etiological factor in a small percentage of cases, but considers congestion and inflammation of the ovary as a more important factor.

Following the demonstration by Allen and Corner (1) that an active extract of corpus lutem could be prepared, our attention was directed to

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the possibility of determining, experimentally, histological criteria of the action of the ovarian hormones separately and in combination. A large series of castrated female mice received varying amounts of oestrin and

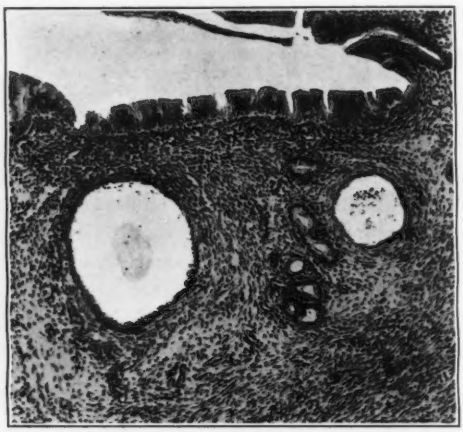

Figure 1. Section of uterus of guinea pig subjected to extreme partial castration for 90 days.

extract of corpus luteum, separately and in combination (2). A comparison of the experimental material with that of the human, both normal and pathological, has made it quite clear that the cellular reaction found in human hyperplasia is quite similar to that invoked by oestrin in the experi-

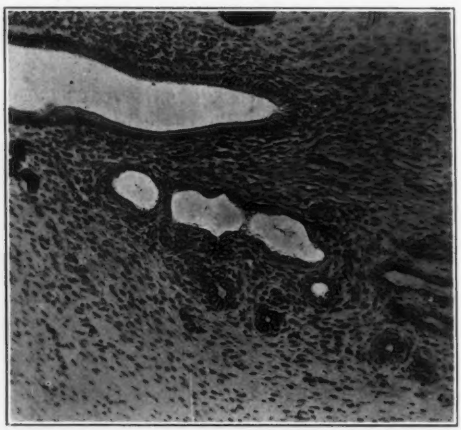

Figure 2. Section of uterus of rat subjected to partial castration for 87 days.

mental animals. This conception was further strengthened by the material obtained from the cysts of two patients which, when injected into mice, produced the typical cellular reaction of hyperplasia.

While the typical cellular reactions were present in all instances, the characteristic cystic dilatation was not observed in any of our injected animals. In view of these conclusive findings, it seemed that this cystic dilatation of Swiss-cheese appearance of the glands was of secondary importance and was probably the result of a long-continued action of the hormone. Shortly before our paper was published there appeared a paper by Fluhmann (5), who approached the problem from much the same point of view and came to practically the same conclusion.

As the cystic dilatation of the uterine glands is an important characteristic of hyperplasia, we felt that further study was important to see if we could produce this change, in addition to the more important changes in the epithelial and stromal cells. In order to further test our hypothesis that an oestrin excess is the etiological factor in hyperplasia, we spayed 20 rats and 24 guinea pigs and injected them with various preparations of oestrin. In order that no peculiarity of the extracts could be considered as a factor, different brands‡ were used.

The amount of oestrin injected averaged 25 units per day and the average duration of the experiment was three weeks. Specimens were col-

Figure 3. Section of uterus of guinea pig which had received 50 units of oestrin daily for 14 days.

leted from the animals by operations performed during the course of the experiments. In a very high percentage of cases cystic glandular dilatation, as well as the characteristic cellular response, was obtained. It certainly needs no great stretch of the imagination to see the similarity between our experimental hyperplasia and the typical human hyperplasia, and one may reasonably conclude that the two represent the same process.

‡We are indebted to E. R. Squibb & Son and to Parke, Davis & Company for the oestrus-producing extracts used in these experiments.

From time to time animals have been observed in the laboratory which normally ran irregular oestral cycles; many of these also showed prolonged oestrus periods. A majority of these have shown, at autopsy, cystic ovaries and hyperplastic changes of the endometrium. It therefore seems quite clear that the condition appears spontaneously in rodents as well as in women.

Since the condition occurs spontaneously in animals, and since it can be produced by an excess of oestrin, it seemed possible that it might be reproduced by means which would lead to an irregular oestral cycle with prolonged oestral periods. Haterius (8) has shown that in partially castrated animals the incidence of prolonged oestrus is increased. Emery (4) has shown that the same is true in rats subjected to unilateral castration. Due to the fact that the ovarian capacity is probably decreased by this method and that hyperplasia usually occurs at the menopause when it

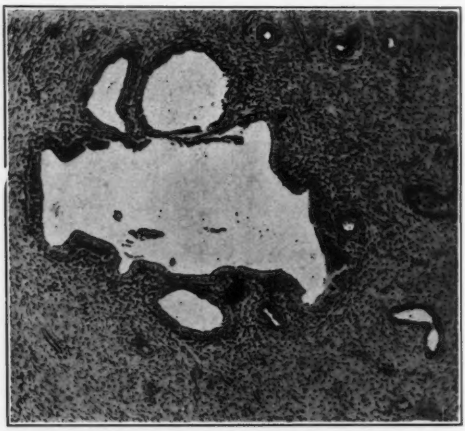

Figure 4. Section of uterus of rat which had received 5 units of oestrin daily for 17 days.

should be decreased, we were greatly impressed with the possibility of this method. Furthermore, in our experience it has not been at all uncommon to have patients, who had one ovary removed previously, return with hyperplasia. This point has not been previously stressed, and we consider it of great practical importance.

Because of the observations cited above, we decided to examine the effect of markedly reducing the amount of ovarian tissue on the endometrium. In preparing the animals for these experiments, one ovary and a portion of the other were removed. Due to the small size of the ovary, it was impossible to remove an exactly equal portion from each animal. A few of our animals did not again come into oestrus, while others came into oestrus regularly. In the former instance, too much ovarian tissue had been removed, and in the latter not enough. In many instances we were

able to produce cystic ovaries (without corpora lutea) and hyperplastic changes in the endometrium; continuous cornification was frequently observed in these animals. These changes are most noticeable in animals which have been operated on six to eight months before they were sacrificed.

DISCUSSION

The production of a condition with a histological picture similar to that seen in human endometrial hyperplasia occurs in rats and guinea pigs following the continuous administration of oestrin preparations. This confirms our previous opinion (2) and is evidence that there is in subjects of that disorder a relative excess of oestrin production in the ovary. However, this does not mean that there is hypersecretion or absolute increase of oestrin; indeed, the secretion may well be within the normal limits and conceivably below normal limits.

We have produced experimental hyperplasia in animals by subjecting them to partial castration; these animals usually presented a continuous oestrus. The explanation of the cause of continous oestrus, as a result of partial castration, is not entirely clear at the present time. Oestrin depresses the ovarian stimulating capacity of the anterior lobe of the hypophysis and the anterior lobe increases the oestrogenic activity of the ovary. Alterations of the hypophyseal-ovarian relationship may well be looked to as the explanation of the altered glandular function resulting in hyperplasia of the endometrium.

SUMMMARY

From previous work done in this laboratory with injections of oestrin and corpus luteum, separately and in combination, it was determined that the cellular reactions of human endometrial hyperplasia were quite similar to those produced by oestrin injections. In none of the animals upon which the experiments were made was the characteristic "Swiss-cheese" dilatation produced. Experiments in which 20 rats and 24 guinea pigs were injected with varying amounts of oestrin for an average period of three weeks are reported. A large percentage of these animals showed the characteristic cellular reactions, as well as the Swiss-cheese dilatations of the glands. Such specimens were very similar to those seen in human hyperplasia. A further series was reported in which the condition was produced as the result of continuous oestrus produced by partial castration. The authors have clinical evidence that such an occurrence is a factor in the production of the condition in the human.

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ON THE STIMULATION OF NEW BONE-FORMATION WITH PARATHYROID EXTRACT AND IRRADIATED ERGOSTEROL

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We have indicated in a previous paper (1) that parathyroid hormone overdosage does not always lead to bone-resorption, but may sometimes produce bone apposition. We were able to show that rats receiving parathyroid hormone in daily injections over long periods have markedly denser bones than their untreated litter mates. The pathological picture of these bones is very suggestive of marble-bone disease, as described by Albers-Schoenberg. The apposition of new bone tissue is in fact most active in the metaphysis of the long bones just as in marble-bone disease, the shaft being practically normal. Therefore we suggested that marble-bone disease may be due to a special form of hyperparathyroidism. This theory seems to be supported also by a recent publication of Pehu, Policard and Dufourt (2). These authors describe a case of typical marble-bone disease combined with an enlargement of the parathyroids. The bone-marrow of this case showed fibrous transformation in some places, which also indicates a condition of hyperparathyroidism.

The new bone formation as produced proves to be due to a change in the reaction of the animals to parathyroid hormone after a period of previous treatment. Whereas the hormone when administered in large doses first leads to bone resorption by osteoclasts and thereby to disappearance of bone tissue, the same substance leads surprisingly, after a certain time of previous treatment, to a contrary effect: that is to say, to new bone formation and thereby to an increased density of the bone, as was shown in our experiments as mentioned above. We cannot confirm the opinion of some authors, that the parathyroid hormone induces a certain immunity in animals and in man treated with it for a longer period. The hormone does not lose its activity after a certain time of treatment but the treated organism reacts differently to the introduced hormone from the untreated organism, for it responds with osteoclast formation in the first stage of treatment and with osteoblast formation in the second. The fact that the organism is not immune is clearly demonstrated by some of the experiments to be referred to in this paper, where osteoblastic reaction in the bone was demonstrable even after very long periods of previous treatment.

Although we see that it is true that the previously treated organism tolerates doses of parathormone which would kill untreated animals, we cannot speak of immunity but only of a state of increased parathyroid-hormone tolerance.

As it would be of great practical importance if we could stimulate new bone formation by pharmacological agents, we studied this question more carefully especially in order to establish the condition under which bone apposition can be stimulated without any damage to the organism.

Because of the close relation between the parathyroid hormone and irradiated ergosterol, we wondered if a chronic overdosage with the latter substance could not produce similar changes in the bones. A recent work of Schmidtmann (13) also seemed to point in this direction for she found that chronic overdosage with irradiated ergosterol may increase the density of the cortical tissue of the bones and at the same time lead to the formation of fusiform and giant cells so that a condition results which is suggestive of osteitis fibrosa.

Therefore, in parallelism with parathyroid hormone, we carried out a series of experiments with Viosterol in order to compare the effect of these two substances on the bones in the same animal under identical laboratory conditions.

I. EXPERIMENTS ON THE STIMULATION OF NEW BONE FORMATION BY LONG CONTINUED ADMINISTRATION OF LARGE AMOUNTS OF PARATHORMONE

Our experiments carried out on albino rats showed that the effect of parathyroid hormone overdosage on the bones may be divided into two distinct stages when sublethal doses are administered. During the first stage fibrous transformation of the bone marrow and the formation of numerous osteoclasts can be seen. These osteoclasts lead to bone resorption, and thereby mobilize the calcium of the bones. Numerous calcium deposits in the various organs appear at this time. When the injections are continued the animals pass into the stage of so-called immunity to parathyroid hormone. In this second stage of hyperparathyroidism the bone marrow becomes entirely different. The osteoclasts disappear and osteoblasts take their place. These osteoblasts lead to bone apposition.

Fig. 1 shows the macroscopical picture of the femur of a rat weighing 60 grams, which received 20 units of parathormone (Eli Lilly and Co.) daily by intraperitoneal injection over a period of 17 days. The metaphyses of these bones are much denser than those of the untreated litter mate.

Fig. 2 shows that this increased density in which large doses of the extract which would kill previously untreated animals are tolerated without any apparent harmful effect, is to be ascribed to the formation of many new trabeculae in the spongy tissue. The number of trabeculae is considerably greater than in the untreated control shown in Fig. 3.

Fig. 4 shows under higher magnification the great number of osteoblasts which surround these bone trabeculae. This picture is obviously quite different from that of osteitis fibrosa, as described by Jaffe, Bodansky and Blair (3), (4), (5), and shown in Fig. 5.

Figure 1. Macroscopical picture of the femur of a rat treated with parathormone for a long period. The metaphysis is much denser than that of the accompanying litter mate control.

Figure 2. Microscopical picture of the femur of a rat with chronic experimental hyperparathyroidism. This plate shows that the increased density of such bones is to be ascribed to the formation of many new trabeculae, especially in the metaphysis.

Figure 3. Untreated litter mate of the rat shown in Figure 2. Here the trabeculae in the metaphysis are present in normal amounts.

Figure 4. Higher magnification of the trabeculae formed under prolonged parathyroid-hormone administration. An epithelium-like layer of oesteoblasts surrounds the new formed bone trabeculae.

Figure 5. Osteitis fibrosa, the result of acute hyperparathyroidism. Marrow fibrosis, numerous osteoclasts (seen at this magnification as large black spots in the fibrous marrow) and disappearance of the bone trabeculae.

We have of course to keep in mind that our rats (as control animals killed during the first few days of the experiments showed) had first to go through a stage of osteitis fibrosa during which bone resorption took place. It was only later that parathyroid hormone tolerance was established in them and new bone formation began.

These experiments seem to indicate that the so-called *"parathyroid hormone immunity" is due to the disappearance of the osteoclasts and the formation of a large number of osteoblasts which prevents a further mobilization of calcium from the skeleton and even leads to an increased calcium deposition in the bones.* Recent experiments carried out by Pugsley (6) in this field, are in accord with this view of the action of parathormone. Pugsley found that the calcium excretion of rats treated with parathyroid extract over long periods increased at first, but later decreased even to subnormal levels. These results and also the hitherto unexplained observation of Bauer, Aub and Albright (7), who found by x-ray examination that the bones of rats treated with parathyroid extract were denser than those of the controls, are in all probability also due to the appearance of the second stage of hyperparathyroidism, the osteoblastic reaction.

Recently, Bodansky and Jaffe (8) studied the increased resistance to parathormone of dogs previously treated with this extract and found that such animals do not show hypercalcaemia, but very often hypocalcaemia after the injection of the hormone. They attribute these findings to a depletion of the calcium stores in the bones and call the condition crypthyperparathyroidism. We think that this unusual reaction to parathyroid

hormone cannot be due simply to the depletion of the bones in calcium because a diminution of the calcium reserve of the body does not explain why the blood calcium should be lowered after parathyroid administration. In view of the histological findings mentioned above it seems likely that the formation of osteoblasts which occurs after parathyroid administration under these conditions leads to bone apposition and thereby removes calcium from the blood into the bones.

Before going further in the description of our experiments we want to mention that the parathyroid hormone has a very definite action on the epiphyseal junction cartilage. In a previous paper (14) we have pointed out already that in very young animals the junction cartilage is enlarged and the cell columns irregular after parathyroid hormone administration and pictures result which are similar to rickets. In the large experimental material used for the present study we had an opportunity to investigate these changes on a larger scale in animals of different age. We found that in older animals the condition may be very different from rickets. The enlargement of the cartilage is often very irregular and when present on one side of the epiphysis may be lacking on the other (Fig. 6). More-

Figure 6. Femur of a rat with chronic experimental hyperparathyroidism. The junction cartilege is very irregular. Formation of very numerous bone trabeculae especially in the metaphysis.

over the matrix often shows areas of degeneration in many places between the cell columns (Fig. 7). These areas frequently show definite fibrous structure. Later the matrix is very much reduced and almost the whole epiphyseal cartilage is composed of irregularly distributed cells. Toward the diaphysis it is possible to follow the cartilage matrix far down in the metaphysis though the cell capsules are opened and invaded by vessels (Fig. 8). This condition is most probably due to deficient resorption of the matrix after the cell capsules are opened and invaded by the primary marrow.

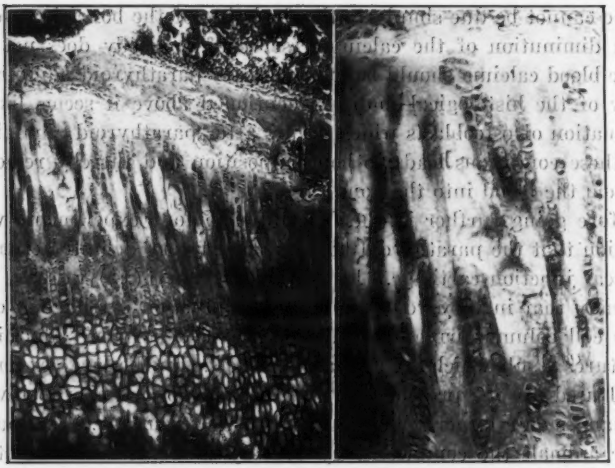

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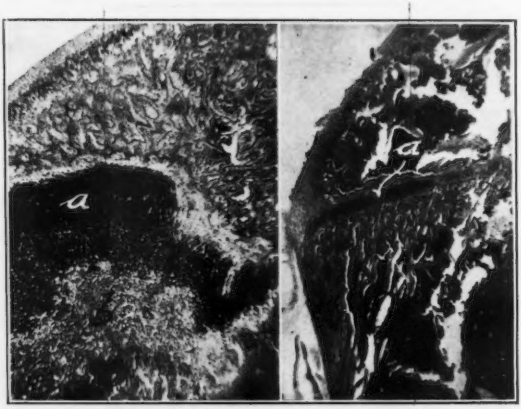
Figure 7. A—Junction cartilage of a rat treated with parathormone. Areas of cartilage matrix, degeneration between the cell columns. The degenerated parts do not stain well and are therefore light in this picture.
B—High power magnification of these areas of matrix degeneration.



A B

Figure 8. A—High power magnification of the distal end of the femur represented in Figure 6.
(a) Points to the very irregular junction cartilage.
(b) Subepiphyseal region. The dark circles are the remnants of cartilage matrix not resorbed as is the case normally by the invading vessels.
B—Distal end of the femur of an untreated litter mate of the animal represented in figure A under the same magnification.
(a) Points to the regular normal epiphyseal cartilage.

H. THE DIRECT STIMULATION OF NEW BONE FORMATION WITH PARATHYROID HORMONE WITHOUT FIRST PASSING THROUGH A STAGE OF OSTEITIS FIBROSA

In this series of experiments we tried to bring the animals into the second or osteoblastic stage without first producing osteoclast formation and osteitis fibrosa. This could be achieved by the administration of very small doses of the hormone.

Figure 9. Femur of rat, which received small amounts of parathyroid hormone. The bone trabeculae are surrounded by hypertrophied osteoblasts.

Fig. 9 shows the femur of an albino rat, 30 days of age, treated with 5 units of parathormone every second day over a period of 5 days. If we compare this picture with the femur of the litter mate control shown in Fig. 10, we can readily recognize that the osteoblasts of the experimental animal are distinctly larger and more numerous than those of the normal

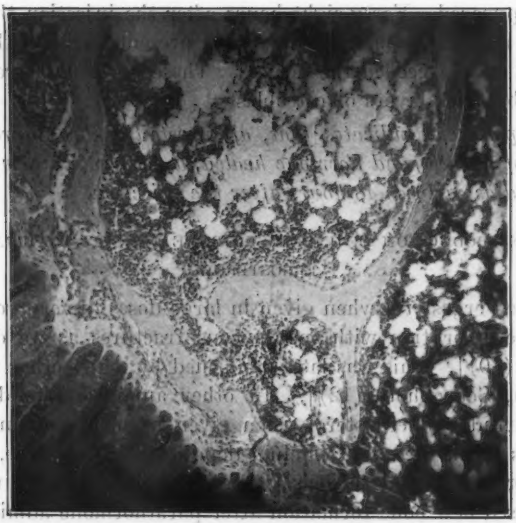


Figure 10. Control litter mate of rat represented in Figure 9. The osteoblasts are smaller and not so numerous.

control. The bone marrow however does not show any signs of osteitis fibrosa nor any formation of osteoclasts.

This experiment shows, that *if parathyroid hormone is administered in very small doses it will lead to a stimulation of the osteoblasts and thereby to bone apposition without previous osteoclast formation and fibrous transformation of the bone marrow.*

III. THE STIMULATION OF NEW BONE FORMATION WITH A SINGLE DOSE OF PARATHYROID HORMONE

It seemed to be of importance to study the effect of a single dose of parathyroid hormone at different intervals. Jaffe and Bodansky showed on guinea pigs that osteitis fibrosa will develop in these animals in a few hours after injection. It was desired to ascertain if after the osteitis fibrosa has disappeared, the osteoblast formation will progress in the same exaggerated way, as is the case in the stage of parathyroid hormone tolerance in animals that have passed in the course of a longer treatment through a stage of osteitis fibrosa.

In this experiment we used a family of 14 day old rats. One of these was killed as a control and the others were all injected with 10 units of parathormone. Then the animals were killed at regular intervals and the bones examined histologically. The first definite changes appeared 6 hours after the injection. At this time a proliferation of fusiform osteoblasts could be seen as well in the spongy tissue of the metaphysis as on the inner surface of the femur shaft. Twenty hours after the injection the typical picture of osteitis fibrosa appeared. The spongy tissue of the metaphysis contained numerous osteoclasts and the majority of the trabeculae disappeared. Forty-eight hours after the injection the osteoblasts disappeared and the bone trabeculae were present again at this time in a number that even exceeded the normal. These trabeculae are surrounded everywhere by thick layers of osteoblasts.

This experiment indicates that, after osteitis fibrosa produced by a single dose of parathyroid hormone healed, a very active new bone formation appeared as early as 48 hours after the injection.

IV. THE PRODUCTION OF INCREASED BONE DENSITY BY IRRADIATED ERGOSTEROL

Irradiated ergosterol when given in large doses to very young animals leads to bone resorption with spontaneous fractures as we demonstrated [Selye, (9), (10)]. This was later confirmed by many other investigators [Comel (11), Schoenholz (12)]. In other animals Schmidtmann (13) found that irradiated ergosterol when given in small amounts over long periods leads to an increased calcium deposition in the bone, the cortical tissue getting denser and thicker. These changes reminded us somewhat of the increased new bone formation after parathormone administration as described above and therefore we tried to study these changes more care-

fully and to compare them with these. We used for the experiment irradiated ergosterol containing 10,000 rat units per cc. The experiment was run on 16 twenty-four day old rats. Similarly to our experiments with the parathyroid hormone we injected viosterol subcutaneously in gradually increasing doses, giving first 0.1 cc. daily during 3 days, then 0.5; after four days again 0.5 cc. and after a week 1 cc., then on the 18th day all the animals were killed.

Macroscopically we found that the bones of these rats are much denser than those of the controls, especially the spongy tissue of the metaphysis was replaced by compact bone with the exception of the subepiphyseal region which frequently contained a little amount of spongy tissue. In some animals the bones were broader than normal, and as this enlargement also took place first of all in the metaphyses, the bones had a club-like appearance (See Fig. 11). As this description shows, the macroscopical aspect of

A B

Figure 11. A—Distal end of a femur of a rat treated with viosterol. Club shaped bone with dense metaphyseal spongy tissue and thick shaft. The epiphyseal cartilage is narrow.
B—Femur of untreated litter mate of the rat represented in Figure A. Same magnification.

these bones was extremely similar to that observed after chronic parathyroid hormone overdosage. Histologically, however, the picture of these bones was very different from that of the parathormone treated animals. There was no increased osteoblast formation, the osteoblasts and osteoclasts being present in practically normal amounts. The bone marrow was of a lymphoid type. The epiphyseal cartilage was extremely narrow and irregular. The zone of preliminary calcification was well developed in some parts, and totally absent in others in one and the same bone. The subepiphyseal zone was composed of small amounts of spongy tissue whereas the rest of the metaphysis contained only compact bone. This compact

bone was necrotic in some cases in the central parts of the metaphysis. The bone trabeculae were usually surrounded by thick osteoid layers (See Figs. 12 and 13).

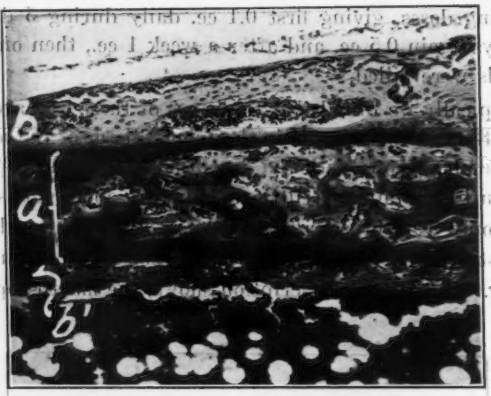


Figure 12. Shaft of the femur in chronic viosterol overdosage.
(a) Deeply stained outlines of the original shaft.
(b) Newly apposited subperiosteal osteoid layer.
(b') Newly apposited osteoid layer on the inner surface of the shaft.

Figure 13. Irregular junction cartilage of the femur in chronic viosterol overdosage. In this section stained with v. Kossa's method, the calcified parts are black.
(a) Indicates the zone of preliminary calcification. The calcium deposition in this layer occurred only on two small spots in the middle of the section. The light seams around the bone trabeculae correspond to the uncalcified osteoid tissue. The white areas are empty marrow spaces (frozen section).

In undecalcified sections stained with v. Kossa method the sites of the calcium depositions are clearly demonstrated by thick silver precipitations. In Fig. 13, we show a sample of a bone section stained in this way. The

irregular calcification of the preliminary calcified zone in the epiphyseal cartilage is easily recognized. The enlargement of the shaft was very much less conspicuous, though also demonstrable. The contours of the original size of the shaft could still be seen in our sections for in it the calcium content was higher and therefore it had a deeper blue color in partially decalcified slices stained with Ehrlich's hematoxylin. Fig. 12 shows this distinctly. In the middle of the compact shaft bone the deeper stained area of the former limits can easily be recognized and both on the periosteal and on the inner wall of this original shaft, thick layers of newly formed osteoid tissue are apposited. Osteoblast hyperplasia is not demonstrable nor is there any marrow fibrosis. But many bone lacunae in the wall of the original shaft are empty. This indicates that the bone cells must have died under the influence of ergosterol. As compensatory new bone formation can frequently be seen around dead bone, the new bone formation in ergosterol intoxication may also be merely of such a compensatory nature. *The microscopic picture of these bones is, as we see, quite different from that seen in chronic parathyroid hormone overdosage.*

SUMMARY AND CONCLUSIONS

1. It has been shown that parathyroid hormone overdosage in rats previously treated with this hormone does not lead to the formation of osteoclasts and to bone resorption as it does in normal animals, but on the contrary to the formation of osteoblasts and thereby to bone apposition.

2. It has been shown that very small doses of parathyroid hormone stimulate osteoblast formation and lead to bone apposition directly without first producing a stage of osteitis fibrosa.

3. This stimulating effect of the hormone in the formation of osteoblasts may be responsible for the so-called "parathyroid hormone immunity."

4. Definite morphological changes in the junction cartilage are described as a result of parathyroid hormone overdosage.

5. Under certain experimental conditions irradiated ergosterol also led to increased bone density and to an increase of the total size of the bones, but the histological features of these dense bones were definitely different from those produced by parathyroid hormone.

The parathormone and irradiated ergosterol used in these experiments was very kindly supplied by the Eli Lilly and Company and Mead, Johnson & Co., respectively.

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Abstract Department

Autopsy observations on one hundred and sixteen cases of malignant disease, in eighty-nine of which experimental injections of suprarenal cortex (Coffey-Humber) were given. Ball, H. A., Am. J. Cancer, **15**: 1352. 1931. Abst., Ann. Int. Med. **5**: 664.

The 116 cases of malignant disease used in this study were divided into three groups; a basic control series composed of 25 cases of malignant disease, previously examined post-mortem by the author, in which application had been made for extract injection, but in which death had occurred before any extract was administered; a relative control series consisting of 47 cases receiving from 1 to 15 injections, or not more than 10.5 cc. of the experimental adrenal cortex extract; and an experimental observation series consisting of 42 cases in which more than 15 injections, or more than 10.5 cc. of the extract, had been given. Since necrosis and sloughing were the chief anatomical changes claimed by Coffey and Humber in their patent application, these manifestations were watched for especially. Necrosis and sloughing were observed frequently and occasionally seemed to be of greater degree or further extent than one would be led to expect from observation of similar uninjected cases. They occurred, however, without correlation to the total amount of extract injected and the difference in these respects among the three series was too slight to be significant. Likewise, no essential difference in the incidence of necrobiosis was found on microscopical examination, using nuclear fragmentation and "replacement fibrosis" as criteria. In 28% of the 89 cases which had received the extract, metastases were found in the adrenals themselves. No essential change from the usually observed characteristics of malignant tissue in far advanced cases could be determined in the two series that received the experimental suprarenal cortex extract (Coffey-Humber), and there were no significant differences between the series that had received less than 15 injections and that which had received more than that amount of treatment.

Calcification in tuberculosis of suprarenal glands: roentgenographic study in Addison's disease. Ball, R. G., C. H. Greene, J. D. Camp and L. G. Rowntree, J. A. M. A. **98**: 954. 1932. Abst., A. M. A.

The authors present six cases of Addison's disease in which roentgenographic shadows in the region of one or of both suprarenal glands were observed. From their study they conclude that lesions of the suprarenal glands are roentgenographically demonstrable in a certain proportion of cases in which there is tuberculous involvement. The more chronic pathologic changes, with fibrocaseation or calcification, appear to be most easily demonstrated roentgenologically. In the majority of cases the active disease process probably destroys sufficient cortical tissue to cause death before fibrocaseation or calcification occurs. In the cases of Addison's disease due to simple cortical atrophy, the roentgenograms obviously would be negative. From a clinical consideration of the group of cases that is sometimes called "borderline" or "questionable" Addison's disease, positive roentgenographic evidence would be a valuable link in the chain. It would seem advisable, in that group of cases in which many symptoms of Addison's disease are present and yet in which the clinician hesitates to make a diagnosis of Addison's disease, carefully to study the suprarenal region roentgenologically. Roentgenologic demonstration of calcification in the region of the suprarenal glands may be of diagnostic significance in a case of suspected or questionable Addison's disease. On the other hand, it must be remembered that suprarenal tuberculosis of marked degree, especially if unilateral, may be present without sufficient clinical evidence of suprarenal insufficiency to warrant a diagnosis of Addison's disease. In reporting six cases of Addison's disease with roentgenographic shadows in the region of the suprarenal glands, the authors hope that further interest will be aroused in the subject. From a study of the available pathologic material it appears probable that in a considerable percentage of cases calcification is present and that this can be roentgenologically demonstrated in life. It is suggested that such a demonstration may be of diagnostic and prognostic significance, and it is urged that roentgenographic studies be made in cases of suspected or proved Addison's disease.

✔ **The oral administration of cortico-adrenal extract.** Britton, S. W., J. C. Flippin and H. Silvette, Am. J. Physiol. **99:** 44. 1931.

The effectiveness of cortico-adrenal extract by mouth is demonstrated. It prolongs considerably and possibly indefinitely the lives of adrenalectomized cats, and brings about complete recovery from even the severest symptoms of adrenal insufficiency, when given by the oral route. The low blood-sugar values found in adrenalectomized animals are markedly increased, and the high non-protein nitrogen values and blood cell volumes are reduced towards or to the normal levels, during the recovery period. Animals that have refused food may be induced to eat within an hour after extract administration. These observations are in keeping with those produced by intraperitoneal injection of the material. Large amounts of the extract were necessary by mouth, approximately three to five times the intraperitoneal dosage, in order to produce comparable results.—From Authors' Abst.

On the "sympathetic substances" obtained from the gut and other organs of the toad. Chang, H. C. and Y. P. Chen, Chinese J. Physiol. **5:** 363. 1931.

A "sympathetic substance" (sympathin?) has been removed from the unstimulated toad's gastro-intestinal tract; on stimulating the sympathetic nerve to the gut a larger yield is obtained. The substance augments the toad's heart, raises blood pressure but has no action on intestinal motility in the dog. Extracts of toad adrenal tissue exert the strongest effect of all and in addition inhibit intestinal motility. The action of extracts obtained in an identical manner from the other tissues, viz., heart, lung, and skeletal muscle of the toad, is similar, but weaker. The identity of these substances remain for further study.—Authors' Summary.

The effects of absinthe on the cat, following bilateral adrenalectomy. Coombs, H. C., S. B. Wortis and F. H. Pike, Bull. Neurol. Inst., New York, **1:** 145. 1931. Abst., Arch. Neurol. & Psychiat. **26:** 650.

This work was done in an attempt to determine the effect of bilateral removal of the adrenal glands on the reaction of animals to a convulsive agent such as absinthe. It was suggested by earlier work on cerebral anemia, which had indicated that general convulsive seizures of unknown origin are caused by vascular changes and that the product of adrenal activity is closely related to the sympathetic mechanism of the vascular system. The experiments were made on a series of cats, and it was found that the minimum convulsive dose was lowered from 33 to 50% by adrenalectomy, while the lethal dose was even more greatly reduced. The results were interpreted as further evidence that removal of the adrenal glands increases cerebral anemia, and they agree essentially with the earlier work of Coombs in 1926.

The induction of precocious sexual maturity by cortico-adrenal extract. Corey, E. L. and S. W. Britton, Am. J. Physiol. **99:** 33. 1931.

Precocious maturation of the sex glands of young albino rats has been produced by the injection of cortico-adrenal extract (Swingle-Pfiffner) prepared in the authors' laboratory. Marked effects were observed in the ovaries of 28-day-old animals. The appearances of early maturity in the testes were not so striking, and occurred later. Hypertrophy of the pituitary gland, especially of the anterior lobe, appeared in 20-day-old rats. The possibility that the effects on the gonads are secondary to enhanced pituitary secretion is entertained. No significant changes were found in the thyroid or the adrenal glands, either in size or structural relationships. An increase in weight in excess of that of control rats was observed in animals injected with the extract. The probability that at least two hormones may be derived from the cortico-adrenal tissues is further discussed.—Authors' Summary.

The calorigenic action of epinephrine in frogs before and after hepatectomy. C. F. Cori and K. W. Buchwald, J. Biol. Chem. **92:** 367. 1931.

Following the injection of epinephrine into immobilized frogs, the oxygen consumption rose on an average 51% in the first and 33% in the second hour, with a return to the basal level in the third hour. The total extra oxygen used during this period was 28 cc. per kgm. of frog, while the extra oxygen calcu-

lated from the difference in aerobic and anaerobic lactic acid formation on the basis of a 4 to 1 reconversion ratio amounted to 25.3 cc. In immobilized and hepatectomized frogs the extra oxygen consumption after epinephrine injection was 18 cc. per kgm. or 35% less than in immobilized frogs with the liver intact. On the second and third day after removal of the liver as the condition of the animal declined, the calorigenic action of the epinephrine became progressively weaker. The sugar content of hepatectomized frogs did not rise when epinephrine was injected; there was, however, an increase in the lactic acid content. It is assumed that the calorigenic action of epinephrine in frogs is due to an accelerated lactic formation with subsequent reconversion of this lactic acid in muscle and liver, a process which is known to be accompanied by expenditure of oxidative energy.—K. W. Buchwald.

Influence of epinephrine and insulin injections on hexosephosphate content of muscle. Cori, C. F. and G. T. Cori, J. Biol. Chem. **94**: 581. 1931.

The average hexosephosphate content of muscle removed from the living animal under amytal was found to be 53.3 mgm. per cent as hexose and 8.9% as P, while the P calculated from the hexose was 9.2 mgm. When the hexosephosphate content of muscle is increased by means of various procedures, the agreement between P determined and P calculated from the hexose content is equally satisfactory. Following subcutaneous injection of epinephrine the hexosephosphate content of muscle is increased after 15 minutes, reaches its peak after 1 hour (109 mgm. per cent as hexose), and slowly returns to the basal level 4 hours after the injection. Insulin injections in fasted rats are followed by an increase in hexosephosphate. When the hypoglycemia is prevented by simultaneous administration of glucose or when insulin is injected into adrenalectomized animals, producing a severe hypoglycemia, the hexosephosphate content of muscle remains unchanged. Hence, it is a secondary output of epinephrine which is responsible for the increase in hexosephosphate during insulin hypoglycemia. Hydrolysis curves of the muscle extract in 1N HCl gave practically identical values under the different experimental conditions mentioned. There was no indication of an accumulation of hexosediphosphate (of the Harden-Young type) during insulin or epinephrine action, nor was any P split off from adenosinetriphosphate. Glucose feeding did not lead to changes in the hexosephosphate content in muscle. While the temporary decrease in blood and urinary phosphate after epinephrine or insulin injection might be due to the accumulation of hexosephosphate in muscle, this explanation does not hold for the decrease in phosphate excretion observed after a carbohydrate meal.—Authors' Abst.

Recurrent hyperthyroidism, neurocirculatory asthenia and peptic ulcer. Treatment by operation on the suprarenal sympathetic system. Crile, G. W., J. A. M. A. **97**: 1616. 1931. Abst., A. M. A.

Thus far the author has performed 104 operations on the suprarenal-sympathetic system. His first unilateral suprarenalectomy among a series of 46 was performed Oct. 1, 1913—eighteen years ago. At that time he held that in diseases due to excessive energy transformation the drive of the so-called kinetic system could be diminished by partial thyroidectomy, by unilateral suprarenalectomy and by excision of the sympathetic ganglions. He soon realized, however, that the value of thyroidectomy was limited strictly to cases of hyperthyroidism, that both lobes had to be resected or recurrence would ensue, and that in this disease occasional recurrences were seen. The same principle of compensatory function was soon noted in unilateral suprarenalectomy. Better results were obtained by a general dekineticizing operation; namely, the removal of one suprarenal, resection of the thyroid, and the excision of the cervical ganglions at the time of the thyroidectomy. Following these patients over a period of years and projecting new lines of investigation, he found that a more commanding operation was a bilateral denervation of the suprarenal glands, the second denervation being performed a week or more after the first one. This operation will relieve and probably cure recurrent hyperthyroidism; it will relieve and probably cure with equal promptness neurocirculatory asthenia, which is a unit of pathologic physiology analogous to exophthalmic goiter. In the diseases in which emotional states, nervous strain, worry and overwork are dominating factors, such as peptic ulcer and diabetes, the principle of the operation may apply; and while the results thus far are encouraging, they are not yet worked out as completely as are those for recur-

rent hyperthyroidism and neurocirculatory asthenia. Time and critical examination of clinical results will bring the final verdict. The author's endeavor, at this early stage, is to present the conception of an energy system which involves a group of organs that collaborate in the transformation of potential into kinetic energy. The excessive driving of this energy-controlling group or kinetic system he designates as pathologic physiology, and the surgical interventions leading to a lessening of the pathologic drive he calls a dekineticizing operation.

Stimulating action exerted peripherally on cellular metabolism by adrenin. Antagonistic action of ergotamine (Action stimulante périphérique de l'adrénaline sur le métabolisme cellulaire. Influence antagoniste de l'ergotamine). von Euler, U. S., Compt. rend. Soc. de biol. **108:** 246. 1931.

The isolated hind paw of a dog was artificially perfused. Oxygen consumption was measured. When adrenin was added to the perfusing blood so as to give a dilution of 10-9 or 10-10 there was a steady rise in metabolic rate. Greater concentrations show an initial fall in rate followed by a rise. If ergotamine is added to the blood before the adrenin the latter does not affect metabolism.—J. C. D.

Muscular fatigue in rabbits surviving double adrenalectomy (La fatigue musculaire chez les lapins survivant a la double capsulectomie). Ferreira de Mira, M. and J. Fontes, Compt. rend. Soc. de biol. **107:** 1167. 1931.

Three rabbits were decapsulated. Two received two consecutive subcutaneous grafts of adrenal tissue which was removed at the end of a month. The other animal received one graft which was not removed. All were killed at the end of two months, during which they appeared normal. Autopsy showed no adrenal tissue. Their muscles showed a normal fatigue curve and not the rapid exhaustion characteristic of decapsulated animals.—J. C. D.

The vital hormone of the adrenal cortex. Hartman, F. A., B. D. Bowen, G. W. Thorn and C. W. Greene, Ann. Int. Med. **5:** 439. 1931.

A potent cortical extract has been administered in two cases of practically complete adrenal insufficiency. In the first case it was of undoubted benefit. Following its use the patient recovered from a very critical state. That it kept him alive for nearly eight months was indicated by four definite relapses which followed its reduction or its discontinuance. Readministration or increase of dosage in each relapse was followed by return to his former level. He was making slow but definite improvement when bronchopneumonia caused his death. The period of treatment in the second case was obviously too short for observation to be of any value. A subject much less severely affected has shown a remarkable increase in her ability to work without fatigue. Clinical improvement has not kept pace with this increase. One subject of hyperthyroidism has exhibited decided clinical improvement following the use of the extract alone. In two cases of muscular atrophy and one of muscular dystrophy some improvement followed treatment. Some evidence was obtained that cortical extract reduces the asthenia which follows certain infections.—R. G. H.

Extract of adrenal cortex protects decapsulated rats against toxins (L'extrait cortico-surrénal protège les rats surrénaloprives contre les toxiques). Houssay, B. A. and A. D. Marenzi, Compt. rend. Soc. de biol. **107:** 1199. 1931.

White rats survive decapsulation but show increased susceptibility to toxins. Thirty-two such rats injected with Swingle and Pfiffner's extract showed a very striking increase of resistance to morphine and histamine poisoning when compared with decapsulated controls.—J. C. D.

Treatment of adrenal cortical obesity. Koster, H., M. Goldzicher, W. S. Collins and A. W. Victor, Am. J. Surg. **131:** 311. 1931.

Koster, et al., emphasize the fact that there is a definite syndrome produced by adrenal cortical hyperplasia. In the adult this condition results in obesity and changes in the secondary sexual characteristics toward the male line, such as hirsutism, thickening of the skin and changes in the voice. They

report a case of a female of 23 years of age who weighed 350 pounds, 125 pounds of which had been gained, despite the administration of thyroid, during the year prior to admission to the hospital. She also had the masculine distribution of hair over her body, a thick, coarse skin and a deep voice. A diagnosis of an adrenal cortical obesity was made. A laparotomy disclosed a bilateral hypertrophy of both adrenals (about 3 times normal), the left being larger than the right. The left adrenal was removed, and the patient made an uneventful recovery. She lost between 15 to 20 pounds of weight monthly and on October 8, 1930 (about one year post-operative), she weighed 190 pounds.—H. Koster.

Tumors of the adrenal gland. Lazarus, J. A. and A. A. Eisenberg, J. Urol. **27**: 1. 1932.

This is a review, with numerous illustrations, of our knowledge of adrenal tumors and a report of two cases of paraganglioma studied by the authors. —J. C. D.

On the nature and structure of the suprarenal cortex. McGowan, J. P., Edinburgh M. J. **37**: 545. 1930. Abst., Biol. Absts. **6**: 3869.

Certain appearances of the suprarenals of fowls suffering from leucosis have led to deductions regarding the structure and function of its tissues. The occurrence of a myelocytic proliferation in the sinusoids would seem to be an instance of the general rule that myeloid tissue is formed in endothelial or subendothelial situations in veins. The cortical nodules are considered to be periarterial structures and to be formed in the mature gland by the development of the reticulo-endothelial elements in the sheaths of arterioles. The cells of the cortex, therefore, are mesoblastic in origin. As regards their function ordinarily in the sex complex, it has been suggested elsewhere by McGowan that, while the interstitial cells of the male and female gonad regulate the sex characters, the cells of the suprarenal cortex have a wider function in that they compel the soma of the individual to conform to the type represented by the indifferent germ epithelium. They act, thus, as the architects for the construction of the neutral soma. As they have no contact with the germ cells subsequent to the original one, it is presumed that the essence, incorporated then, is passed on hereditarily from cell to cell in division. As the indifferent germ epithelium of the germinal ridge disappears, it would seem that the interests of the species must be entrusted to some persisting organ. The view advanced here is that this is the suprarenal cortex.

Effect of intravenous injections of adrenin on rabbits' heart. Terminal fibrillation. Electrocardiographic studies (Action de l'adrénaline en injection intraveineuse sur le coeur du lapin. Fibrillation cardiaque terminale. Etude électrocardiographiques). Petzetakis, M., Compt. rend. Soc. de biol. **106**: 885. 1931.

Adrenin affects the chronotropic, bathmotropic, dromotropic and inotropic properties of the cardiac muscle. The effect lasts five to twenty minutes. Lethal doses produce auricular fibrillation followed by fatal ventricular fibrillation.—J. C. D.

New form of Hodgkin-Paltauf-Sternberg's disease; Addison's syndrome and granulomatosis (Una nueva forma clinica de la enfermedad de Hodgkin-Paltauf-Sternberg: Granulomatosis a forma addisoniana). Ruiz, R., Rev. sudam. de endocrinol. **14**: 499. 1931. Abst., J. A. M. A. **97**: 1498.

Ruiz reports the clinical history of a tuberculous and syphilitic man aged 47, in whom nearly all the manifest disorders, such as pigmentation of the skin with hyperpigmentation of the mucous membranes, asthenia and low blood pressure, indicated Addison's syndrome. The patient had also fever, convulsions of an ischemic origin and adenopathy. He died and the necropsy revealed that all these changes had been caused by a spleno-lumbo-aortic granulomatosis. The author supports Spangenberg's opinion on the advisability of regarding certain forms of granulomatosis simulating Addison's disease as a new clinical type of tuberculosis. The clinical picture of the type coincides with the symptomatology given by the author's patient. Sympathetic and en-

docrine factors play a part in the pathogenesis of the disease (in the author's case lesions of the solar plexus complicating a dysfunctioning of the cortex of the suprarenals were found). In order to reach a clear diagnosis it is necessary first to make a differential diagnosis between Addison's syndrome and a pseudosyndrome resembling Addison's disease. Since the two principal symptoms of Addison's syndrome are typical asthenia and skin pigmentation, the fact that one of the symptoms is nontypical indicates the presence of a pseudosyndrome, which, if complemented by the positive diagnosis for granulomatosis, gives the clear diagnosis of the new type of granulomatosis. The determination of the blood formula and the biopsy of a lymph node (repeated if necessary) will help to make the precise diagnosis of granulomatosis. The treatment of this clinical type should be the same as that for general granulomatosis. Medical and surgical treatments have been resorted to in granulomatosis without success, though the evolution of the disease is not rapid. Roentgen treatment has given the best results.

The suprarenal-genital syndrome of Cooke-Apert-Gallais (Le syndrome surreno-genital de Cooke-Apert-Gallais). Schereschewsky, N. Rev. franc. d'endocrinol. **9**: 103. 1931.

Schereschewsky reports the case of a 12-year-old girl who complained of headaches, vertigo, great increase of weight and enlargement of the right ear. The family history showed endocrine stigmata in the grandparents, also a history of alcoholism in the grandparents. He states that the diagnosis of the case presented many difficulties as she showed many endocrine stigmata: (1) Development. (2) Obesity. (3) Hypertrichosis. (4) Retardation in development of the sex organs. (5) Symptoms pertaining to the nervous system such as vertigo and dizziness. He then analyzed the different symptoms and tried to fit it in with different glandular conditions and finally concluded that it belonged to the syndrome of Cooke-Apert and Gallais. This symptom complex consists of symptoms associated with internal hydrocephalus in hirsutism. The first observation was made by Cooke in 1796, in which he observed obesity in hypertrichosis but the triad virilism, hirsutism and amenorrhea were described by Apert and Gallais, Guthrie and many others. Cooke described many other symptoms which accompanied this syndrome such as hypertension with glycosuria. Precocious development of the genitals is usually not encountered but one usually observes atrophy of the genital organs. Tachycardia and palpitation is sometimes described. Increased cholesterol of the blood has been described. Schereschewsky believes that it is a neuro-pluriglandular symptom complex due to alteration in the vegetative nervous system of the brain with internal hydrocephalus.—R. C. Moehlig.

Studies on the adrenal cortex; further observations on preparation and chemical properties of cortical hormone. Swingle, W.W. and J. J. Pfiffner, Am. J. Physiol. **98**: 144. 1931.

Extract made from whole adrenal glands is as effective in combating adrenal insufficiency and as low in adrenalin content as are preparations of cortex alone. A new method for separation of adrenalin from the cortical hormone is described. It consists in distributing an active fraction between aqueous alkali and an immiscible solvent such as benzene or ether. Adrenalin passes into solution in the aqueous alkali, whereas the cortical hormone is found in the immiscible solvent phase. By means of the above fractionation step, highly active extracts (1 cc. equivalent to 30 grams of cortex) have been prepared, containing less than one part of adrenalin in 4,000,000. The cortical hormone is thermolabile and is destroyed by boiling an active extract in an open flask for two minutes. Cortical extracts prepared with permutit fractionation give a negative biuret, ninhydrin, Hopkins-Cole, Molisch, Pauly and Liebermann-Burchard reaction. They give a positive xanthoproteic, Millon's alkaline copper, and alkaline phosphotungstate reaction. These four positive reactions can be accounted for by the presence of traces of phenolic decomposition products of adrenalin. Cortical extracts, if preserved with 0.1% benzoic acid, retain their potency for long periods at room temperature. Tests of the potency of fractions containing the cortical hormone which had been stored in benzene for 12 to 15 months, show that they retained much of their activity during this period, although they are apparently somewhat less potent than freshly prepared material.—Authors' Summary.

Secretion of adrenin following stimulation of the cranial and spinal meninges (Adrénalino-sécrétion par excitation des méninges crâniennes et rachidiennes). Tournade, A., H. Hermann and J. Malmejac, Compt. rend. Soc. de biol. **106:** 1149. 1931.

In dogs connected with one another by vascular anastomosis it can be shown that stimulation of the dura-mater in the one dog is followed by a splenic contraction in the other. This indicates a slight increase in adrenin output in the first dog.—J. C. D.

The suprarenals and tissue residual nitrogen (Die Beeinflussung des Rest-N-Spiegels im Organismus durch die Nebennieren). Will, G., Arch. f. exper. Path. u. Pharmakol. **160:** 317. 1931. Abst., Physiol. Absts. **16:** 561.

The residual nitrogen content of the tissue in rabbits increases after extirpation of the suprarenals. Preliminary administration of urea also increases the residual nitrogen of the tissues. Larger doses of adrenalin also increase the tissue residual nitrogen, and this is even more marked after the preliminary giving of urea. This adrenalin effect is only found when the suprarenal cortical hormone is present, since in suprarenalectomized animals adrenalin causes no further increase in the residual nitrogen than would be found as the effect of the suprarenalectomy alone.

The blood sugar response to epinephrin in thyroid fed animals. Abbott, A. J. and F. W. Van Buskirk, Am. J. M. Sc. **182:** 610. 1931.

Feeding 2.55 gms. of desiccated thyroid to 1 rabbit over a period of 21 days resulted in a progressive loss of body weight, decrease in the hyperglycemic response to epinephrin and, finally, an absence of hyperglycemic response, similar to the findings of Burn and Marks, and Marks, with a fatal hypoglycemic response to epinephrin when the liver glycogen was apparently depleted. The feeding to 3 cats of 31, 82 and 70 gms. of desiccated thyroid, over a period of 15, 35 and 27 days, respectively, resulted in loss of body weight, but no definite decrease in the hyperglycemic response to epinephrin. The feeding to 2 dogs of 280 and 647 gms. of desiccated thyroid, over a period of 50 and 37 days, respectively, resulted in no definite loss of body weight and no definite decrease in the hyperglycemic response to epinephrin. It is probable, for the reasons outlined in the body of the paper, that the hyperglycemic response to epinephrin in dogs and cats indicated that the liver glycogen had not been depleted by thyroid feeding under the conditions of the experiment. Though we hesitate to draw basic conclusions because of the limited number of experiments, the results at least show the great resistance of dogs and cats to thyroid. The reaction of these species is probably an exception. Since man is more sensitive than animals to thyroid, it would seem likely that the liver glycogen may decrease in man more as it does in the rabbit than as in the resistant dog and cat, but it is obviously impossible to prove this in man.
—Authors' Summary.

The action of the anterior pituitary upon the secretory activity of the thyroid (L'hormone prehypophysaire excito-secretrice de la thyroide). Aron, M., Rev. franç. d'endocrinol. **8:** 472. 1930.

Fresh anterior lobe when injected stimulates both the secretive and excretive actions of the thyroid, somewhat on a quantitative basis, within limits, of course. The colloid disappears rapidly, there is then an augmentation of volume as well as of weight of the thyroid and hyper-conditions are established. The author concludes that activity of the thyroid in a normal body is conditioned if not controlled by a hormone secretion from the anterior body.
—B. C.

Endocrines and coxa vara of adolescents (Les troubles endocrines dans la coxa vara essentielle des adolescents). Beau, A., Rev. franç. d'endocrinol. **9:** 192. 1931.

An attempt to relate abnormal bone development in coxa vara to endocrine glands. The disease, of course, cannot be cured by treatment but might have been avoided by a proper endocrine balance.—B. C.

The action of epinephrine and insulin in frogs under anaerobic conditions. K. W. Buchwald and C. F. Cori, J. Biol. Chem. **92**: 355. 1931.

Epinephrine injections increased the sugar and lactic acid content of frogs under aerobic as well as anaerobic conditions. When epinephrine was injected into frogs which had received insulin 18 hours to 42 hours previously, an increase in sugar content did not take place either aerobically or anaerobically. This effect of insulin is ascribed to an inhibitory action on hepatic glycogenolysis, being especially noticeable when the latter is augmented by epinephrine or anaerobosis. The fact that epinephrine is able to accelerate lactic acid formation under anaerobic conditions argues against the idea that this effect is due to vasoconstriction and hence to asphyxia in muscle. The evidence is in favor of the assumption that epinephrine has a direct accelerating effect on glycogenolytic process in muscle.—K. W. Buchwald.

The endocrine function of the salivary glands (La fonction endocrine des glandes salivary glands). Cahane, M. and F. Cahane, Rev. franç. d'endocrinol. **8**: 398. 1930.

Work of others is assembled to indicate that the parotid glands have endocrine functions.—B. C.

Follicular, luteinic and mammarian incretotherapy and its influence on the genital tract and on the endocrine system. Experimental study (Incretoterapia follicolare, luteinica, mammaria e sue influenze sul tratto genitale e sul sistema endocrino. [Studio esperimentale]). Candela, N., Arch. di ostet. e ginec. **17**: 97. 1930. Abst., Am. J. Obst. & Gynec. **22**: 657.

The author, from studies on guinea pigs treated with follicular, luteinic and mammarian extracts, arrives at the following results. The follicular extract is responsible for a more accentuated development of the genital tract, the maturation of the ovarian follicles and the prolongation and intensification of the estrus cycle; the other extracts may determine alterations in the rhythm of the estrus cycle or else in its suppression; the mammarian extract may lead to atrophy of the ovary and of the genital tract. The thyroid and the mammary gland are slightly hypertrophied with the follicular extracts, this condition is more marked with luteinic and mammarian extracts. Notable hypertrophy is also obtained in the suprarenals and in the hypophysis by the action of the follicular and mammarian extracts. With the luteinic extracts, on the other hand, there is obtained atrophy of the hypophysis and moderate hypertrophy of the suprarenals. Finally, the luteinic and mammarian extracts lead to an increase in weight of the animal, but confer sterility. The follicular extract has no influence on the body weight and augments fecundability.

The effect of hypoglycemia on cellular activity of the anterior and posterior lobes of the hypophysis and the tuber cinereum (Action histo-physiologique de l'hypoglycémie sur la glande pituitaire, la neurhypophyse et le tuber cinereum).

The effect of hypoglycemia on cellular activity of the thyroid, parathyroids, pancreas, salivary glands and thymus (Action histophysiologique de l'hypoglycémie sur les glandes thyroïde et parathyroïdes, le pancréas, les glandes salivaires et le thymus).

The effect of hypoglycemia on cellular activity of the spleen and adrenals (Action histophysiologique de l'hypoglycémie sur le foie, la rate et les glandes surrénales). Collin, R., P. L. Drouet, J. Watrin and P. Florentin, Compt. rend. Soc. de biol. **108**: 61; 64; 66. 1931.

Guinea pigs were given insulin. The hypophysis and the thyroid responded with signs of increased activity. The medulla of the adrenal enlarged regularly while the cortex was hypertrophied as in pregnancy. The authors outline the chain of events as follows. Insulin provokes a discharge of adrenin from the adrenal medulla. This causes an outpouring of colloid from the hypophysis into the circulation and the tuber cinereum. The activity of the hypophysis stimulates the thyroid to activity in the course of a week. The increased thyroid output causes an atrophy of the thymus and hyperplasia of the islands of Langerhans.—J. C. D.

The mechanism for hyperglycemia following lumbar sympathectomy in dogs (Sur le mécanisme de l'hyperglycémie après sympathectomie lombaire chez le chien). Fontaine, R. and L. G. Herrmann, Compt. rend. Soc. de biol. **106**: 1063. 1931.

This increase in blood sugar is not interfered with by removal of both adrenals, the ablation of the solar plexus or the peripancreatico duodenal plexus but is eliminated by total pancreatectomy.—J. C. D.

Excessive ultra-violet irradiation; effect on the nutrition and the endocrine glands of rats. Hess, A. F. and P. E. Smith, Am. J. Dis. Child. **41**: 775. 1931.

Two series of rats were irradiated with the mercury vapor lamp or were given viosterol for a period of from five to six months. The main object of the experiment was to note whether prolonged and intensive irradiation or large doses of viosterol had a deleterious effect on the animals as evidenced by the rate of growth and by the size and appearance of the endocrine glands. The growth of the animals subjected to marked intensities of ultra violet irradiation or given large amounts of viosterol was as good as that of animals which had lived under similar conditions but had not been subjected to irradiation or given viosterol. No difference was noted at necropsy between the endocrine glands of the treated and those of the untreated animals.—M. B. G.

Relation of endocrine disorders to industrial medicine. Hutton, J. H., Illinois M. J. **60**: 62. 1931.

In this interesting paper the author concludes that ovarian insufficiency is undoubtedly a cause of much absenteeism among female employees. This absenteeism could undoubtedly be reduced by a considerable percentage if industry surveyed its women workers and instituted the proper treatment. Thyroid deficiency is common, particularly in this climate, and is to blame for the condition of many workers who are able to deliver only a few hours of efficient work per day because of their easy fatigability and low physical reserve. Many neurasthenics are victims of undiscovered, many times unsought for, endocrine disorders. Cases of hypertension, particularly in the obese, should have the benefit of a careful search for endocrine disorders. Many cardiac disturbances, particularly auricular fibrillation, myocarditis, and extrasystole, are due to endocrine disorders, particularly thyroid, ovarian, and adrenal—I. B.

Condition of the thyroids of pigeons fed desiccated anterior hypophysis (Der Zustand der Schildrüse von Tauben bei Fütterung mit Pituikrin "A"). Larionov, W. T. and O. Kotowa, Endokrinologie, **9**: 264. 1931.

Earlier studies had shown that feeding desiccated thyroid tissue alone produces in doves a hypoplastic thyroid with a low flat epithelium, and induces the moulting of feathers. Also, that daily feeding of dried anterior lobe tissue has an opposite effect, since it produces a hyperplastic thyroid with a high epithelium, and has no moult-promoting effect. It is now found that when thyroid administration (30-60 mgm. daily per bird) is accompanied by the daily feeding of somewhat larger amounts of anterior lobe powder (30-240 mgm.) the typical action of the anterior lobe substance is expressed within and throughout the thyroid, and that the typical action of the desiccated thyroid dosage is expressed by its unchanged power to produce moulting of feathers. It is thus shown that a chemical combination of thyroxin and pituikrin did not result from their simultaneous administration. Concerning Pituikrin "A" it is stated only that "it is a powder-like preparation of the anterior lobe which is prepared in the Institute for Experimental Endocrinology in Moscow."—O. Riddle.

The effect of starvation, phloridzin, thyroid, adrenalin, insulin and pituitrin on the distribution of glycogen in the rat. Lawrence, R. D. and R. A. McCance, Biochem. J. **25**: 570. 1931.

Starvation does not reduce the glycogen of the heart, kidney or stomach. Phloridzin reduces the glycogen of the liver and muscles slightly below starvation level, but has no effect on that of the heart, stomach or kidney. Thyroid extract by mouth reduces very greatly the glycogen of the heart. The hyperthyroid heart is unable to replenish its glycogen stores even after high carbo-

hydrate feeding. After 24 hours' starvation the hyperthyroid liver contains only slightly less glycogen than the control, but has completely lost the normal ability to store glycogen after carbohydrate food. The hyperthyroid 24 hours' starved muscle contains slightly less glycogen than the normal, but storage is quite normal after carbohydrate ingestion. The heart glycogen is the first to be depleted by thyroid. Adrenaline increases the liver-glycogen and decreases the muscle-glycogen of starved animals. It has no effect on the glycogen of other organs. Insulin has no effect on the glycogen of heart, stomach or kidney. It reduces liver and muscle-glycogen of the fasting rat.

—Authors' Summary.

The respiratory metabolism in infancy and in childhood. XII. A biometric study of basal metabolism in normal infants. Levine, S. E. and E. Marples, Am. J. Dis. Child. **41:** 1332. 1931.

Biometric analysis confirms the validity of the commonly accepted standards of Benedict and Talbot for estimating the basal metabolism of these subects and indicates that of all their standards those referred to stature are probably the most reliable for prediction. The study demonstrates the independent influence of age, weight, height and body surface on the mechanism of heat production during infancy. In normal infants, the relation of metabolism to age per se is apparently trivial. The evidence does not appear adequate to establish the view that the sexes differ in their metabolic response during the period of infancy. The similarity of predictions when made either from the multiple regression equation incorporating the physical factors, body weight and height, or from body surface as estimated by the height-weight formula of DuBois and DuBois (Hannon) attest the reliability of the latter procedure for the estimation of this measurement in infants of normal body contour. A nomogram is presented for predicting the basal metabolism of normal infants from two physical characters, body weight and stature. It must be emphasized that it has no decided superiority over the standards of Benedict and Talbot referred to height when applied to infants of normal build. It may possess advantages over standards referred to a single physical character in interpreting metabolic measurements of infants of exceptional body conformation. This phase of the subject will be considered in a subsequent communication. It should be pointed out that the results of the biometric analysis presented in this study, in common with the standards of Benedict and Talbot, are applicable for purposes of predicting basal metabolism solely in normal infants. Their validity is considerably reduced when applied to infants of exceptional body contour.—M. B. G.

Effect of folliculin on the anterior lobe of the hypophysis (Action de la folliculine sur le lobe antérieur de l'hypophyse).

Folliculin and the endocrine glands: thyroid, adrenal, spleen, and liver (Folliculine et glandes a sécrétion interne: thyroide, surrénales, rate, foie). Montpellier, J. and L. Chiapponi, Compt. rend. Soc. de biol. **104:** 373; 375. 1930.

Normal female rats injected with five units per day for about five months showed no hypophyseal changes. In castrated male and female rats, after the same treatment, the histological picture of the anterior lobe was that of an uncastrated animal, not that of a castrate. No change took place in the histology of the thyroid, adrenals, spleen, or liver.—J. C. D.

Ductless glands as they appertain to eye diseases and to surgery. Ruedemann, A. D., J. A. M. A. **97:** 1700. 1931. Abst., A. M. A.

As conclusions to his article, the author enumerates the following noteworthy facts: (1) Frequently it is found that patients who are examined for glasses have a muscle imbalance which may be due to hypothyroidism or other glandular dysfunction. (2) Hyperthyroidism produces definite eye changes, which in most cases are benefited by surgery; namely, wide fissures, ulcers and exophthalmos. Associated muscle changes are little benefited by any treatment, medical or surgical. (3) In parathyroid tetany, lens changes are sometimes present, probably the result of a combination of spasm with a deficiency of calcium and phosphorus. (4) Dysfunction of the pituitary gland is a causative factor in certain retinal disturbances and is an associated factor in other eye changes probably of polyglandular origin. (5) The recent work of Crile also brings out a group of cases in which suprarenal dysfunction is associated with eye changes.

Enlargement and hyperplasia of the thyroids in the young duck from the injection of anterior pituitary. Schockaert, J. A., Am. J. Anat. **49:** (No. 3). 1932.

Series of injections of an anterior-pituitary suspension, a purified growth hormone (phyone), luteinizing hormon (Squibb), and prolan were made in young, immature ducks and effects upon the thyroids observed. Some controls were untreated and others injected with spleen emulsion. The suspension and purified growth hormone caused a marked enlargement of the thyroid, the suspension giving the greater effect. A relative increase of sixty times was secured in one case, the usual increase being, however, three to eight times. Correlated structural changes resulted. Shorter periods of treatment produced little change in size of vesicles, but the colloid disappeared and the epithelium became of a high columnar type showing many pycnotic nuclei, desquamation, and mitoses. In more prolonged treatment the vesicles enlarged, the epithelium became folded, and some colloid, which was granular and stained faintly, was formed. These thyroids are very similar structurally to the thyroids in Basedow's disease. A marked drop in thyroid iodine and exophthalmos were evident. Thyroids of animals injected with the luteinizing hormone and prolan did not differ from those of the spleen-injected controls. Thyroids of the latter and, to a lesser extent, those of untreated controls also showed some enlargement and hyperplasia in animals which were kept for three weeks or longer in the laboratory. These effects were always much less pronounced, however, than those in animals treated with pituitary suspension and phyone.—Author's Abst.

Studies in the physiology of exercise. IV. Further concerning exercise and basal metabolism in dogs. Steinhaus, A. H. and T. A. Jenkins, Am. J. Physiol. **95:** 202. 1930.

Basal metabolism data gathered in the latter three years of a five-year study on three male dogs observed in and out of exercised states is presented and analyzed. Dietary additions for the purpose of supporting the body weight during exercise were marked by increases in basal metabolism. This is in accord with the findings of others. When care is taken to distinguish between effects due to exercise and those due to the increased food intake, the observations lend further evidence to the view that an extended period of training which puts the animal in excellent athletic condition is without noticeable effect on the basal metabolism per square meter per 24 hours. It is proposed that the high degree of relaxation which is acquired by the trained animal may explain why it is possible to have muscle hypertrophy without an increased basal metabolic rate. Marked spontaneous fluctuations around averages often much lower than those reported for normal dogs are noted. A position is developed which would explain the appearance of greater fluctuations coincident with the attainment of more nearly true basal conditions. There is some indication that the fluctuations are cyclic in nature. Whatever their cause it is clear that any study of the effects of drugs, hormones or other factors on the basal metabolism must in some way reckon with these fluctuations. In the present work this was done: (1) by extending the observations over a long period of time; and (2) by holding at least one and usually two dogs as untreated controls to reflect the nature, trend, and extent of the spontaneous variations.—Authors' Summary.

The part played by the endocrine glands in active immunity (Die Rolle der endokrinen Drüsen in der aktiven Immunität). Stschedrowitzky, S. G., E. Lopatina and A. Korabelnikowa, J. Medico-Biologique, **2:** 60. 1930.

This investigation has to do with the part played by the endocrine glands in the formation of antibodies. In rabbits the glands were extirpated singly and in pairs in 200 different experiments upon 39 animals. In thyroidectomized animals the formation of antibodies is noticeably restricted both immediately after the operation as well as for six months after. In castrated animals the agglutinizing power was reduced only after 2 or 3 months have elapsed. No difference was seen between castrated and normal animals immediately after the operation. In castrated and thyroidectomized animals the transplanting of corresponding glands causes an increase in the agglutinizing power. Immunization of castrated, thyroidectomized animals by simultaneous

injection of blood, restricts almost completely the return of the agglutinizing power. Subsequent castration does not affect the agglutinizing ability of thyroidectomized animals. Extirpation of the parathyroids of castrated animals causes a stimulation of the antibody formation.—J. Gagnon.

Is the increase in insulin which follows injections with adrenalin of pancreatic origin (L'hyperinsulinémie consécutive a l'injection d'adrénaline est-elle d'origine pancréatique)? Zunz, E. and J. La Barre, Compt. rend. Soc. de biol. **106**: 1241. 1931.

The carotid of dog A was connected to the pancreatic artery of dog B. The pancreas of dog B was denervated and drained into the circulation of dog C, who was decapsulated. Following the adrenin injections into dog A there was, in three out of five cases, a reduction of blood sugar in dog C. This could only result from an increased output of insulin due to direct stimulation of the gland by the adrenin in the blood of dog A.—J. C. D.

Endocrine activity of ovary. Allen, E., J. A. M. A. **97**: 1189. 1931. Abst., A. M. A.

According to the author, the only sound basis for therapeutic treatment of menstrual disorders with hormones is a broad foundation of experimental evidence concerning the endocrine activity of the ovaries. He summarizes the recent work on follicular and corpus luteum hormones and sketches in outline a conception of the factors responsible for the periodic changes in the genital organs during the menstrual cycle. Attention is called to the fact that it has been shown in many animal experiments that the follicular hormone does not stimulate the development of follicles in the ovaries. Consequently primary hypo-ovarian conditions should probably be treated with anterior hypophysis extract when that is purified and biologically standardized. In cases of amenorrhea or scanty menstruation of long duration, treatment with follicular hormone has in a certain percentage of cases started cyclic activity which has in some instances persisted after cessation of treatment. In other cases it has not proved effective. Disturbances in the secretion of other endocrine glands, especially the anterior hypophysis and thyroid, should be ruled out before administration of theelin. Several reports have shown that theelin is sometimes effective in the treatment of extreme menopause symptoms, either operative or natural. A declining dose would be indicated in an effort merely to adjust the patient gradually from effects which are undoubtedly due to deficiency of this hormone. Progestin would be indicated for therapeutic use in cases in which repeated difficulty in carrying the embryo through the early stages of gestation is encountered. It might also be used later in pregnancy in combination with theelin to carry on the stimulation of growth in undeveloped mammary glands. First, however, it must be standardized biologically. The matter of the rather difficult test reaction for this active substance, at least compared with that for theelin, will probably postpone the early therapeutic use of progestin.

Histologic changes in the genital tract of castrated male rats following repeated injections of urine from pregnant women (Les modifications histologiques du tractus génital du rat male impubère, a la suite d'injections prolongées d'urine de femme enceinte). Bourg, R., Compt. rend. Soc. de biol. **105**: 232. 1930.

Thirty daily injections of 1 cc. each were given to 30-day-old rats. The testes and the rest of the genital tract were enlarged to almost adult size. Histologically the development of the interstitial tissue and the germinal portions was almost that of an adult.—J. C. D.

Changes in the ovary and genital tract of kittens produced by "gravidine" (Les modifications provoquées par la gravidine au niveau de l'ovaire et du tractus génital de la chatte impubère).

Changes in the testes and genital tract of kittens produced by "gravidine" (Les modifications provoquées par la gravidine au niveau du testicule et du tractus génital du chat impubère). Bourg, R., Compt. rend. Soc. de biol. **106**: 926; 928. 1931.

"Gravidine" is the hormone found in the urine of pregnant women which produces precocious puberty in mice and other animals. In female kittens

injected with 5 cc. of urine for five days those ovarian follicles which were already well developed responded by undergoing abnormal development and cystic dilatation. In the male the response was a marked hypertrophy of the interstitial tissue with no reaction of the tubular epithelium.—J. C. D.

Changes produced by "gravidin" in the genital tract of immature rats studied by vital staining with injections of trypan blue (Les modifications génitales provoquées par la gravidine chez la rate impubère étudiées par la méthode des injections vitales de trypanblau). Bourg, R., Compt. rend. Soc. de biol. **107:** 911. 1931.

The corpora lutea persisting as a result of this treatment can best be described as hypertrophied atretic follicles. The uterine changes suggest those found in pregnancy. The vital stain helps distinguish the elements of the follicles.—J. C. D.

Modifications produced by gravidine in the pregnant and non-pregnant adult cat (Les modifications provoquées par gravidine chez la chatte adulte en dehors de la gestation et durante cette période). Bourg, R., Compt. rend. Soc. de biol. **108:** 216. 1931.

In non-pregnant cats urine from pregnant women produces, when injected, cystic changes in the half-grown follicles of the ovary, death of the oocyte and alteration of the follicle into a cystic corpus luteum. There is also hypertrophy of uterine glands and change in the vagina. In pregnant animals urine injections bring about similar changes in the ovary but there are no changes in the uterus or vagina.—J. C. D.

The preparation of pure follicular hormone from pregnancy urine (Über die Reindarstellung des Follikelhormons aus Schwangerenharn). Butenandt, A., Ztschr. f. physiol. Chem. **196:** 127. 1930.

A method is given of preparation of pure crystalline follicular hormone from commercial extracts of pregnancy urine. The purification proceeds in four steps: (1) extraction of dilute alcohol solution with petroleum ether; (2) extraction of dilute alcohol solution with benzene; (3) separation, utilizing the lactone character of the hormone, with HCl, ether, Na_2CO_3 and NaOH; (4) distillation under high vacuum. It is recrystallized from ethyl acetate and high boiling ligroin.—J. M. Curtis.

The physical and chemical properties of the follicular hormone (Über physikalische und chemische Eigenschaften des krystallisierten Follikelhormons. Butenandt, A., Ztschr. f. physiol. Chem. **196:** 140. 1930.

The crystalline follicular hormone has a formula $C_{18}H_{22}O_2$ and melts at 250°-251° C. (corr.). Acetyl and benzoyl derivatives have been prepared. One hydroxyl group may enolize to form a carbonyl group as shown by the preparation of the oxime. There are three double bonds which have been catalyticly reduced. The analysis of all these derivatives is reported.

—J. M. Curtis.

Effect of castration on the scent glands of the goat (Action de la castration sur les glandes odorantes du bouc). Chatagnon, P., Compt. rend. Soc. de biol. **106:** 631. 1931.

A goat castrated at five months showed an impaired development of horns and an entire lack of male odor derived from the widely distributed cutaneous glands in this form.—J. C. D.

The female sex hormones (Les hormones sexuelles femelles). Courrier, R., Compt. rend. Soc. de biol. **107:** 1367. 1931.

This is a resume of our present knowledge. A selected bibliography of 139 titles covers the American and European literature through 1930.—J. C. D.

Further investigation on the action of folliculin in rabbits carrying corpora lutea (Nouvelles recherches sur l'action de la folliculine chez la lapine en phase lutéinique). Courrier, R. and R. Kehl, Compt. rend. Soc. de biol. **107:** 1547. 1931.

Doses of 300 to 800 rat units in a week given to a rabbit with a corpus luteum produce marked changes in the uterus. There is intense vascular congestion with oedema, hemorrhage, and areas of involution and necrosis. About the vessels appear distended cells. These are usually characteristic of the region where the ovum is implanted but under the present conditions are found all through the uterus.—J. C. D.

Purification of the male hormone by high-vacuum distillation. Dingemanse, E., J. Freud, S. Kober, E. Laqueur and A. P. W. Münch, Proc. Acad. Sci. Amsterdam, **33:** 1206. 1930. Abst., Chem. Abst. **25:** 1887.

The method of fractionation is described and a schematic outline of the fractions obtained is presented. It is concluded that the male hormone can be brought to a high degree of purity through high-vacuum distillation. At 90° with pressure of 0.001 mm. the hormone is found in the distillate, and at 80° in the residue. Fractional distillation offers the possibility for the separation of the male from the female hormone.

Early pregnancy—a hormone test for its diagnosis. Dorn, J. H., Jean R. Morse and E. I. Sugarman, California & West. Med. **35:** 266. 1931.

This paper corroborates the evidence presented by numerous papers on the value of the Aschheim-Zondek test and is based on 150 tests performed by the authors. The conclusions drawn are to the effect that the hormone test as performed on rabbits is accurate to a high degree. The results are specific, giving no false positive reactions, and yielding only very few negative results where positive might have been expected.—I. B.

Treatment by Roentgen rays in ovarian dysfunction. Ford, F. A., Minnesota Med. **13:** 186. 1930. Abst., Am. J. Obst. & Gynec. **22:** 542.

In discussing irradiation of pituitary and ovaries in amenorrhea, oligmenorrhea, menorrhagia, metrorrhagia, and dysmenorrhea, 6 cases are presented in which there was improvement or cure following treatment. Such results, however, can be obtained in only 50% of cases.

Rôle of female sex hormone. Frank, R. T., J. A. M. A. **97:** 1852. 1931. Abst., A. M. A.

According to the author, the female organism, from the neonatal age to the menopause, and perhaps beyond this critical period, is under the influence of the prepituitary hormone and the female sex hormone. After puberty, it is affected at intervals by the progestational hormone. He summarizes these various endocrine influences thus: The anterior lobe hormone stimulates the ovary to produce follicles. The follicle in turn elaborates the female sex hormone, which reaches the tubular tract (tubes, uterus, vagina) by means of the blood stream. The tubular tract, after sufficient blood concentration has been reached, then undergoes the early premenstrual changes. Following ovulation, the corpus luteum develops. This transitory gland continues to produce female sex hormone as well as a special hormone, whose presence in the circulation has not yet been demonstrated, enhancing the local uterine and breast changes necessary for the nidation and early nutrition of the fertilized ovum. Among these changes, sensitization of the uterine mucosa, requisite for successful embedding, is particularly important. If the corpus luteum is removed at this early stage, the ovum fails to secure the necessary firm hold in the endometrium and abortion results. The chorion epithelium, later developing into the placenta, an important gland of internal secretion, takes up the production of both female sex hormone and prepituitary hormone. Probably as a safety factor the circulation is flooded with these two internal secretory products to such a degree that an enormous amount is excreted through the kidneys and bowel throughout pregnancy.

The tetanoid syndrome in pregnancy. Hartley, E. C., Minnesota Med. **13:** 190. 1930. Abst., Am. J. Obst. & Gynec. **22:** 655.

Another case illustrating the tetanoid syndrome in pregnancy is reported by the author. The patient was in her tenth pregnancy, 36 years old, and presented edema of the extremities, insomnia, irritability, crampy pains, and paresthesias that make up the syndrome. Administration of parathormone and calcium produced striking and immediate relief. The condition is probably due to a relative hypocalcemia.

Phylogeny of menstruation. Hartman, C. G., J. A. M. A. **97:** 1863. 1931. Abst., A. M. A.

The author emphasizes the fact that although the general biologist may concede that in its spectacular manifestations menstruation is a "prime character," if one searches for fundamental or even for the more superficial physiologic causes, and if one investigates other mammals and even the lower vertebrates and attempts to discover what they have in common with man, anthropocentric ideas receive jolt after jolt. He shows the universality of uterine bleeding in the vertebrate series and offers this generalization as another example of the kinship of man with the whole of creation. Sufficient is said to introduce those who have not thought of the matter to the widespread occurrence of bleeding into the müllerian derivatives. The study of the control of the bleeding has not yet begun, so far as the lower vertebrates is concerned. The suggestion of Hartman, Firor and Geiling that a hypophyseal factor may be generally involved seems to be worth following up. The common denominator in the physiologic control of the various types of bleeding is likely to be the fundamental principle involved. Menstruation according to this view begins with the Salachian fishes.

Effects of injections of an active material extracted from the corpus luteum on the genital tract of normal and castrated females (Effets d'injections d'une substance active extraite du corps jaune sur le tractus génital de femelles castrées et non castrées). Klein, M., Compt. rend. Soc. de biol. **107:** 1018. 1931.

In castrated and normal rabbits the extract produced a condition in the uterus similar to that normally preceding the implantation of the egg. In the uncastrated animals this change was less marked and the ovarian follicles showed degenerative changes.—J. C. D.

Terminology of the female sexual hormone (Zur Terminologie der weiblichen Sexualhormone). Lipschütz, A., Biochem. Ztschr. **220:** 453. 1930. Abst., Biol. Absts. **6:** 3869.

In the endocrine activities of the ovary there are two phases: the follicular phase (in which folliculin, the estrus-exciting hormone, is formed), and the corpus luteum phase (in which a luteohormone is formed, which is concerned with the implantation of the ovum). It remains to be seen whether there is need to distinguish an a-luteohormone, which governs the growth of the pregnant uterus, and a B-luteohormone, which inhibits estrus. The discovery by Aschheim and Zondek of rut-exciting substances in urine of which it is not yet known whether they are of ovarian or placental origin makes necessary a name by which to identify them without assuming their identity with folliculin. The same applies to the feminizing substances discovered by Loewe, et al., in plants, for which Loewe proposed the name "thelykinine." It is desirable to distinguish the estrus-exciting substance of vegetable origin as such. The most suitable term for the purpose is "estrin," proposed by Parkes and Bellerby for the hormone of the follicular fluid but unsuitable for that purpose because based on function, not on localization. "Estrin" is well adapted to indicate substances of non-ovarian origin which produce follicular action; thus, plants produce so many units of estrin; urine contains estrin. Whether there is an estrin identical with the ovarian folliculin is a question for investigation. Laqueur and Dingemanse have already shown a difference between the folliculin from follicular fluid and the estrin from urine.

On the occurrence of oestrin in the urine of the pregnant cow (Über das Vorkommen von Oestrin im Harn der schwangeren Kuh). Lipschütz, A. and S. Veshnjakov, Biochem. Ztschr. **220:** 456. 1930.

The urine of cows has been treated by the same methods which served for the extraction of follicular hormone from the urine of the pregnant woman.

Oestrin is present in the urine of the pregnant and non-pregnant cow, but only small quantities are found as compared with the amounts in human pregnancy urine. The question arises whether the oestrin in the urine of the cow is identical with the follicular hormone or whether it derives from the oestrogenic substances present in the food of the herbivorous animal.— A. Lipschütz.

Further studies on experimental work on probable causes of prostatic hypertrophy. Lower, W. E. and R. L. Johnston, J. Urol. **26**: 599. 1931.

Recent work indicates that the pituitary acts through the interstitial tissue of the testis to control the size of the prostate. The authors implanted radium in the testes of white rats. This destroyed the tubular tissue but left the interstitial tissue intact. The prostate enlarged. Injections with gonad stimulating hormone of the pituitary were followed by prostatic enlargement. The authors conclude as follows: (1) Certain simple glandular hypertrophies of the prostate which have not passed predominantly into the fibrotic stage may be benefited by suppression of the male hormone, or by suppression of the anterior pituitary gonad-stimulating hormone which regulates the production of the male hormone. (2) Removal of the testes breaks the chain of continuity in this hormone mechanism and causes (a) prevention of further glandular proliferation; (b) atrophic changes and shrinking of the glandular tissue which is already present. (3) Many hypertrophied prostates have already reached a stage which is predominantly fibrotic. In such cases a reduction of the hormone may be of doubtful value. (4) Future research should aim to confirm or deny these findings, and to find less radical means of suppressing the male hormone.—J. C. D.

Immunologic aspects of the sexual cycle; anaphylactic studies with mammalian follicular fluid. Lyons, W. R. and F. R. Van de Carr, Arch. Path. **9**: 1. 1930.

The follicular fluids of the four mammals studied (sow, cow, mare, ewe) are closely related immunologically; they are similarly related to the follicular fluid of the experimental animal, the guinea-pig. Guinea-pig follicular fluid is auto-antigenic. Guinea-pigs artificially sensitized to follicular fluid proteins are temporarily desensitized by the liberation of their own follicular fluid. Fatal anaphylaxis may be produced at a definite time, in normal guinea-pigs, by primary injection of heterologous follicular fluid.—Authors' Summary.

Seminal vesicle grafts in mice (Greffes de vésicules séminales chez la souris). Martins, T. and D. M. Cardoso, Compt. rend. Soc. de biol. **106**: 509. 1931.

Immature seminal vesicles were transplanted into the musculature of the abdominal wall of young male mice. The vesicles grew, matured and produced secretion showing that sufficient testicular hormone is present to stimulate them.—J. C. D.

Gonad hormone functions, and the reciprocal influence between gonads and hypophysis with its bearing on the problem of sex-hormone antagonism. Moore, C. R. and Dorothy Price, Am. J. Anat. **50**: (No. 1). 1932.

Observations are reported on the effects of injecting testis hormone and oestrin singly, and as mixtures, into castrated and normal male and female rats. Also reported are effects from combinations of these two hormones with the additional administration of gonad-stimuating substances from fresh hypophysial homo-implants and extracts of human pregnancy urine. A theory of a reciprocal gonad-hypophysial influence is offered to explain the findings presented and it is extended to include the observations from many other laboratories that involve several different lines of experimentation. Four main conceptions are defended: (1) gonad hormones stimulate homologous sex characters, but are without effect upon heterologous characters; (2) gonad hormones have no direct effect upon the sex glands of either sex; they neither stimulate nor depress the sex glands; (3) gonad-stimulating substances are necessary to force the activity of these organs to produce sex cells or secrete hormone, and, (4) sex hormones (of both sexes) suppress hypophysial function. An explanation of the controlling mechanism of the oestrous cycle is suggested. "Sex-hormone antagonism" does not exist in the adult mammal.—Authors' Abst.

The action of ether extracts of testicular powder on castrated fowls (Sull' azione degli estratti eterei di polvere di testicolo nei galli castrati). Pellegrine, G., Archiv. dello Istituto Biochimico Italiano, **3**: 205. 1931.

The experiments were carried out on capons with three preparations obtained from bulls' testicles. Dried testis-tissue in doses of 2 grams per day, suspended in salt solution and injected, had a slight effect on the rate of regression of the comb and did not cause comb-growth. The ether-extracted powder, when similarly injected, seemed to hasten the rate of regression. The ether-extract of the powder possessed comb-growth-stimulating activity when injected in doses equivalent to 20 to 40 grams of dry tissue. The latter results he considers to confirm substantially the findings of the American workers in this field.—F. C. Koch.

The effect of x-raying one ovary of a rat on a subsequent pregnancy after the removal of the normal ovary during the course of gestation. Pencharz, R. I. and J. A. Long, Am. J. Anat. **50**: (No. 1). 1932.

One ovary in each of 24 rats was brought to the surface through a dorsal incision and x-rayed, care being taken to shield all the rest of the body by means of lead plates. During pregnancy immediately following treatment the untreated ovary was removed. Abortion or resorption followed within 24 to 48 hours in 23 out of the 24 cases. In the twenty-fourth case the normal ovary was removed so late in gestation (nineteenth day) as to make the case comparable to ordinary late ovariectomy. Young were born and suckled until weaned. Control experiments were carried out to check the effects of the operative procedure aside from the action of the x-rays. It was found that mere manipulation and exposure of one ovary, and removal of the opposite ovary during early pregnancy, did not interfere with the normal gestation period. Serial sections of the irradiated ovaries (five cases) showed the presence of what is apparently luteal tissue of unknown age, interstitial tissue, and degenerate follicles containing remains of eggs. The presence of an x-rayed ovary containing the foregoing structures is apparently not sufficient to maintain pregnancy.—R. I. Pencharz.

Therapeutic irradiation of the ovaries. Seifert, A. C., California & West. Med. **35**: 290. 1931. Abst., Arch. Phys. Therapy, **12**: 699.

Radiation therapy directed to the ovaries with a view of the temporary or permanent elimination of their function is safe and economical in many gynecological and general diseases. Roentgen or radium radiation is the treatment of choice in benign menorrhagia, painful menstruation and menses associated with severe systemic symptoms. It may be also termed the treatment of choice in simple uncomplicated or intramural fibromyomata of the uterus not exceeding the size of a three-months' pregnancy. Larger myomata may be treated with the roentgen ray with excellent hopes of success. It is especially indicated where such tumors are complicated by serious renal, cardiovascular, or pulmonary diseases. Of the two agents used in radiation therapy the roentgen ray is the safer and more economical to the patient. Radium is more valuable when the immediate cessation of a uterine hemorrhage is imperative, or when a diagnostic curettage is to be done. The one general and absolute contraindication to all radiation treatment in benign conditions is pregnancy. In treating youthful patients the ovarian function need not be permanently abolished, and this end may be accomplished by careful and accurate dosimetry (dosimeter in vagina, preferably). The question of damage to the offspring arising from the fertilization of a radiated ovum has not yet been settled for the human. The author thinks as a rule women much below forty years should be excluded from radiation therapy whenever possible. Radiation therapy does not exclude subsequent surgery nor render it, as a rule, more difficult. Radium will stop uterine hemorrhage within twenty-four hours even in small doses, the latter by direct action on the endometrium. This is not equivalent to action on the ovary of larger doses. The number of authors is increasing who report favorable results from roentgen irradiation of the ovaries when used in chronic infectious disease of the genital tract. Cessation of the menstrual function through irradiation of the ovaries has a valuable therapeutic effect in carcinoma of the breast, in Graves' disease and in tuberculosis of the lungs.

Rôle of progestin in female reproductive cycle. Smith, G. van S. and O. W. Smith, J. A. M. A. **97:** 1857. 1931. Abst., A. M. A.

The authors outline the functions of progestin and its rôle in the normal human menstrual cycle and in pregnancy. The luteinizing hormone which stimulates the production of progestin was administered by them with promising results, to 19 patients whose chief symptom was abnormal flowing. The authors believe that early clinical and experimental evidence points to another function of progestin; namely, that of inhibiting the production of the follicle hormone and promoting its excretion.

Effect of hypophysectomy on ovulation and corpus luteum formation in rabbit. Smith, P. E. and W. E. White, J. A. M. A. **97:** 1861. 1931. Abst., A. M. A.

The authors hypophysectomized rabbits by a procedure that permits prolonged survival. They noted that ovulation will take place although the pituitary is removed after a postmating period but slightly over an hour in length, thus confirming the report of Fee and Parkes. In such animals the corpora lutea develop normally for approximately a two-day period. Further changes are atypical. The development of the corpora in the absence of any post-ovulatory pituitary secretion is discussed in regard to its bearing on the question of the unity or the duality of the pituitary sex hormones.

Characterization of theelol. Thayer, A., L. Levin and A. Doisy, J. Biol. Chem. **91:** 655. 1931.

Elementary analyses of the crystalline compound indicate the formula $C_{18}H_{32}O$. The molecular weight, by Rast's method, is 294.2; M.P. is 273.8 (uncorr.). Theelol is dextrorotatory, rotation unchanged after 22 hours. The iodine number by special micro method is 86.7, indicating one double bond and molecular weight of 292.8 as compared with theoretical, 288, for $C_{18}H_{32}O_2$. Quantitative estimation of (OH) groups by acetylation shows 3 (OH) groups to be present. Recrystallized triacetyl derivative melts at 126° C. (uncorr.). Mol. Wt.=410. Combustion data agree with theoretical. Distillation of ester in vacuo yields crystalline product having same characteristics. Hydrolysis of distilled ester yields the original theelol. Methylation of theelol yields a monomethyl ether, as determined by combustion and methoxyl determinations.

—Authors' Abst.

The results of the rabbit ovulation test in the diagnosis of pregnancy. Wilson, K. M. and G. W. Corner, Am. J. Obst. & Gynec. **22:** 513. 1931.

The results obtained from the urines of 196 women upon whom the rabbit ovulation test as suggested by Friedman was made are herewith presented. The findings correspond very closely to those reported in the use of the Aschheim-Zondek reaction, with apparently a very small percentage of error. Its advantages over the latter are found chiefly in the much shorter time necessary, its simplicity, and a possible economy of laboratory animals. From our experience we believe that it should prove to be an extremely valuable and practical method for the early diagnosis of pregnancy. In our series, with the exception of a single case of endometrial hyperplasia, a positive reaction has always indicated the presence of active fetal tissue in biologic contact with the maternal blood stream, or very recently (not over seventy-two hours) separated from it. A negative reaction does not entirely exclude the possibility of a pregnancy being present, since the intra- or extra-uterine ovum may have perished, and been retained for some period of time. It may prove to be of some value in determining the life or death of the ovum in the early months, though not its immediate death, and not in the later months of pregnancy.

—Authors' Summary.

The relationship of the increased content of the blood of posterior lobe pituitary hormone to the existence of nephropathy and eclampsia in pregnancy (Über die Beziehung des gesteigerten Gehaltes des Blutes an Hypophysenhinterlappenhormon zur Entstehung der Nephropathie und Eklampsie der Schwangeren). Anselmino, K. J. and F. Hoffmann, Arch. f. Gynäk. **144:** 506. 1931.

Anselmino and Hoffmann attempted to show in this article that the production of nephropathy and eclampsia is produced by an increased secretion of the posterior pituitary lobe. They say that it has been definitely proven

that Hofbauer first, and later Rossenbeck and Küstner proved that there was a change in the function of the posterior lobe and believe this gland to be responsible for the production of eclampsia. The proof that there was an increased function of the posterior lobe has not until now been possible. According to Seitz, toxicosis and eclampsia is due to some metabolic disturbance. It is important, therefore, in studying these cases that we use early mild cases just as we study the metabolism of diabetes in the mild cases and not in those who are already in diabetic coma. The coma and convulsions are not specific manifestations which are present in many other diseases and this also would indicate that the coma and convulsions of eclampsia are end results and do not give us the information concerning the disease any more than the coma of diabetes gives us the basis for understanding the metabolism in diabetics. The pre-eclamptic symptoms of nephritis with hydrops gives us certain information. The outstanding feature of metabolism disturbances in these individuals is the tendency to water retention. From experiments of Zangemeister this is produced by disturbance in water secretion. If one brings this toxicosis in relationship with the internal secretion disturbance, one will see that the increased blood pressure with the vaso pressor substance of the posterior lobe is present. If we compare the important clinical symptoms found in nephropathics and eclamptics with the definite findings of posterior lobe hormone, we find as follows: That after pituitrin injections and water intoxication the animals will have coma and convulsions which simulate eclampsia very closely. In toxicosis, the galvanic excitability is decreased. The same decrease is found in the animals that have received injections of pituitrin. The tendency to capillary spasm in toxicosis is very well known and equally well known is the capillary contracting effect of pituitrin. The effects of pituitrin are decreased in the animals by the same narcotics and hypnotics as seen in Strogonoff's treatment. These considerations and agreement between the working of the posterior lobe secretion and the changes found in nephropathics and eclamptics led to conclusion that there is increase of the posterior lobe secretion in this disease. Of 20 cases of nephropathy and eclampsia examined very closely there was shown an enormous increase of the antidiuretic component of the posterior lobe in 19 of the cases. The amount of increased secretion paralleled the grade of edema present, i.e., the more blood pressure raising component present, the greater the edema. In moderately severe cases there was 4-5 V. E. in a liter of blood. Only in one case of eclampsia were they unable to demonstrate antidiuretic substance of the blood and this case did not have edema. However, in all cases which clinically had a blood pressure of over 180 mgm. of mercury they were able to demonstrate this blood pressure raising principle and among these only one case which did not have the antidiuretic substance. The antidiuretic substance in the blood is identical with the antidiuretic principle. For the blood pressure raising principle in the blood, the absolute proof is still lacking but the identity of the two substances is no doubt probable. Is this internal secretion disturbance confined entirely to the posterior lobe? The thyroid hormone seems in many ways to be antagonistic to the posterior lobe. From tests it was found that the content of the blood of the thyroid hormone in the nephropathic was about half as much as that found in normal pregnant women but in eclamptics a definite increase of thyroid hormone was found but not as much as the increase of the posterior lobe. With this it is shown that the internal secretion disturbance in toxicosis is not confined to the posterior lobe alone but is pluriglandular and the posterior lobe takes a most prominent place in its production.—R. C. Moehlig.

Balance between the hormone of the anterior lobe of the hypophysis and of the thyroid within the body under normal and pathologic conditions (L'équilibre entre l'hormone préhypophysaire et l'hormone thyroïdienne dans le milieu intérieur, a l'état normal et a l'état pathologique). Aron, M., C. Van Caulaert and J. Stahl, Compt. rend. Soc. de biol. **107**: 64. 1931.

In experimental conditions in animals and pathologic conditions in man, an increase in one hormone is accompanied by a decrease in the other.
—J. C. D.

Action of the anterior lobe of the hypophysis on the guinea pig ovary (Action de la préhypophyse sur l'ovaire du cobaye). Aron, M., Compt. rend. Soc. de biol. **108**: 25. 1931.

In immature animals extracts and implants produce a stimulation of the interstitial cells. In mature animals the thecal cells are stimulated. There

was no hastening of maturity or formation of corpora lutea under the influence of anterior lobe extract.—J. C. D.

A new method for the Aschheim-Zondek reaction: Biological and clinical study (Un procede nouveau d'application de la reaction d'Aschheim-Zondek). Bourg, R., Rev. franç. de gynec. et. d'obst. **26**: 65. 1931.

It has been shown by Brouha that the changes in the male may be a satisfactory index of the presence of anterior pituitary hormone (prolan?) in the urine. Bourg suggests the use of male rats in the determination of the Zondek-Aschheim reaction. The changes in the seminal vesicles are exact and easy to detect macroscopically, thus obviating the use of the microscope. Daily inections of 1 cc. of urine are given to young rats, 28 to 40 days of age for 5 days. Rats are preferable to mice for the reason that puberty in rats starts later, approximately at 2½ months. Further, rats are more resistant to the injections and the mortality is low. In 120 rats only two deaths occurred.—B. Parvey.

Metabolism of nitrogen and sugar in fasting dogs after hypophysectomy (Exchanges azotés et glycémie des chiens hypophysoprives a jeun). Braier, B., Compt. rend. Soc. de biol. **107**: 1195. 1931.

Seventeen dogs were hypophysectomized and five more had the tuber cinereum injured. In the latter no metabolic changes were evident. In the hypophysectomized animals during starvation nitrogen elimination is reduced and there is also a marked hypoglycemia, often ending in fatal convulsions. —J. C. D.

Nitrogen output of hypophysectomized dogs on a meat diet (Elimination azotée après un repas de viande chez les chiens hypophysoprives). Braier, B., Compt. rend. Soc. de biol. **108**: 128. 1931.

The hypophysectomized animals eliminated per day per kilo the same amount of nitrogen as the controls. If the animals were fed after a fast, the nitrogen output was less for the first 6-8 hours in the operated animals than in the controls but the total for 24 hours was the same. During starvation the experimental animals eliminated less nitrogen than controls. Damage to the tuber cinereum did not affect nitrogen output.—J. C. D.

Hypophyseal-ovarian relationship. Burch, J. C., W. L. Williams, J. M. Wolfe and R. S. Cunningham, J. A. M. A. **97**: 1859. 1931. Abst., A. M. A.

Experiments described by the authors tend to show that endometrial hyperplasia is due to a relative excess of estrin. This, of course, can result from either an actual excess or a relative excess. The latter seems more probable. The ovary and the hypophysis are closely associated and each affects the other. There is a definite cyclic variation in the capacity of the anterior hypophysis to produce ovulation. Variations and deficiencies in the ovulation cycle might easily cause alterations in the menstrual cycle with idiopathic bleeding as a symptom.

Effects of hypophysectomy on the reproductive system of salamanders. Burns, R. K. and A. Buyse, Anat. Rec. **51**: (No. 3). 1932.

In half-grown specimens of Amblystoma tigrinum (Colorado "axolotl" variety), 12 to 14 cm. in length, the gonads are well differentiated although relatively immature, while the duct systems are in most cases undifferentiated and identical. When hypophysectomized at this time there are degenerative changes in both sexes, which occur in spite of the fact that the subjects ultimately attain adult size. Follicular atresia occurs rapidly in the ovary, and there is atrophy, with marked histological disorganization in the testis. Later, there is partial recovery of the testis with resumption of larval form; while in the ovary only younger ovocytes survive, with many corpora atretica. The ducts remain in approximately the condition in which they were at hypophysectomy. These changes were observed over a period of one year. In a few adults, hypophysectomized under like conditions, there is more acute retrogression of the mature reproductive organs. In the testis degeneration is extreme, while in the ovary only younger ovocytes survive. The ducts also retrogress, but, within the period of the experiment, fail to return completely to the larval condition. The male cloaca behaves like the ducts.—Authors' Abst

A differential stain for the anterior lobe of the hypophysis. Cleveland, R. and J. M. Wolfe, Anat. Rec. **51**: (No. 3). 1932.

A differential stain for the anterior lobe of the hypophysis of mammals, based directly on the Mallory connective-tissue stain and Biedermann's method, has been devised. The block is fixed in Regaud's solution, mordanted in 5% potassium dichromate, dehydrated, and embedded in 60° paraffin. Serial sections are cut at 3 micra, mounted, and dried. After hydration, they are stained for three minutes in Ehrlich's hematoxylin. They are then mordanted in the dark for three days in 3% potassium dichromate, which is changed daily. After being mordanted and washed rapidly in distilled water, they are stained for twenty to thirty seconds in a 0.5% aqueous solution of erythrosin, rinsed through two waters, immersed for two to three minutes in a 1% aqueous solution of phosphomolybdic acid, in 100 cc. of which 2 grams of orange G has been dissolved, rinsed rapidly, and stained in a 1% aqueous solution of aniline blue for one-quarter to one and one-quarter minutes. After treatment with aniline blue, the sections are rapidly dehydrated through 95% and absolute alcohols, cleared in xylol, and mounted in balsam.—Authors' Abst.

The influence of the anterior pituitary hormone on the testicles of guinea pigs (Influenza dell'ormone ipofisario anteriore sui testicoli della cavia). Colombi, C., Boll. d. Soc. ital. di biol. sper. **6**: 423. 1931. Abst., Chem. Absts. **26**: 764.

An increase of the interstitial portion of the testicle takes place in the guinea pig on injecting the sexual hormone contained in the urine of pregnant women. Similar results are obtained if the urine is first shaken with Et_2O to remove the ovarian hormone.

The reaction to posterior pituitary extract (pituitrin) when introduced into the cerebral ventricles. Cushing, H., Proc. Nat. Acad. Sc. **17**: 163. 1931. Abst., Arch. Neurol. & Psychiat. **26**: 1313.

Herring (1908) first described hyaline bodies in the neurohypophysis, believing apparently that they were the secretory product of the epithelial portion of the posterior lobe known as the pars intermedia. Globules appeared to go toward the tuber cinereum and in favorable histologic preparations could be seen passing between the bodies of the ependymal cells to enter the infundibular cavity. Cushing and Goetsch (1910) supported the conception (1) by showing that occlusion of the pituitary stalk served to dam back the secretory product in the pars nervosa, and (2) by demonstrating that the active principle of the lobe was detectable in the spinal fluid. Histologic confirmation of Herring's discovery has been made and has shown that the cells in question, under a nervous stimulus, disgorge their ripened cytoplasm into the pars nervosa and that the extruded product undergoes hyalinoid transformation during its migration into the tuber cinereum. Histologic study has also shown that the posterior part of the pituitary body receives a rich nerve supply from the thalamencephalic centers. The extrusion of hyaline globules into the ventricles has also been observed histologically. Physiologically, it has been shown: (1) that a substance resembling extract of the posterior lobe is often demonstrable in normal ventricular and cisternal but not in lumbar fluids; (2) that it may be increased by the administration of certain organic extracts as well as of drugs, particularly those producing diuresis; (3) that it disappears after hypophysectomy or occlusion of the pituitary stalk; (4) that it is increased by emotional stimuli, and (5) that it is augmented by direct stimulation of the hypothalamus or tuber. McLean expressed the belief that this substance is absorbed initially by the vascular route, finding its way to the cerebrospinal fluid through the choroid plexuses. Karplus was of the opinion, however, that the active principle of the posterior lobe is discharged, at least in part, into the ventricular fluid. Cushing injected solution of pituitary directly into the ventricles in human beings and found that the extract thus injected caused a prompt response characterized by intense flushing from vasodilatation, profuse perspiration, retching and vomiting, salivation, a marked fall in body temperature and a lowering of the basal metabolic rate. There are two possibilities regarding the action of the extract: (1) resorption into the blood stream, and (2) the direct stimulation of hypothalamic nuclei by diffusion of the substance through the ependymal lining of the third ventricle. Of these, the latter is the more probable.

The similarity in the response to posterior lobe extract (pituitrin) and to pilocarpine when injected into the cerebral ventricles. Cushing, H., Proc. Nat. Acad. Sc. **17**: 171. 1931. Abst., Arch. Neurol. & Psychiat. **26**: 1314.

Solution of pituitary, when injected into the ventricles, produces a reaction so similar to that of pilocarpine that Cushing decided to make comparative studies of the two drugs. Both drugs produce flushing, sweating with salivation and lacrimation, retching and vomiting. The chief differences between the two lay (1) in a more marked vagal effect from pilocarpine, with continued retching and vomiting, as compared with only a brief period of nausea with solution of pituitary, and (2) in a more pronounced fall in body temperature from pituitary. Both of these substances give reactions that suggest a parasympathetic (bulbar) rather than a sympathetic (thoracolumbar) stimulation that is central in origin.

The sexual hormone of the pituitary. Actions on female animals (Die Mehrheit der Sexualhormone der Hypophyse; Wirkung auf weibliche Tiere). Dingemanse, E. and S. E. de Jongh, Pflüger's Arch. f. d. ges. Physiol. **226**: 543. 1931. Abst., Physiol. Absts. **16**: 492.

Confirmatory evidence has been obtained in experiments on rats and mice for the presence of 2 gonadotropic substances (causing follicular maturation and luteinization respectively, and corresponding to Prolan A and B described by Zondek and Aschheim) in pregnancy urine.

Comparative effect of vasopressin and pituitrin on intestinal peristalsis (Action comparée de la vasopressine et de la pituitrin sur le péristaltisme intestinal). Action of ocytocin on peristalsis and the antagonism between vasopressin and ocytocin (Action de l'ocytocine sur le péristaltisme intestinal et antagonisme entre la vasopressine et l'ocytocine). Elmer, A. W. and L. Ptaszek, Compt. rend. Soc. de biol. **104**: 540; 542. 1930.

Vasopressin causes a marked increase in peristaltic activity in both small and large intestine. It is much more active than pituitrin and can be employed to a greater advantage in paralytic ileus. The relative lack of effect of pituitrin on peristalsis can be explained, since ocytocin has an inhibitory effect on intestinal movement and when mixed with vasopressin reduces the influence of the latter.—J. C. D.

Histological changes in the liver and kidneys after intoxication with extracts of the posterior lobe of the hypophysis (Histologische Veränderungen am Leber und Nieren nach Intoxikationen mit Hypophysenhinterlappenextrakten). Fauvet, E., Arch. f. Gynäk. **144**: 502. 1931.

There are certain facts which show that there is a close relationship between nephritic edema and the eclamptic symptom complex. Eclampsia is characterized clinically by convulsions and the pathological-anatomical changes of a typical nature in the liver and kidneys. It is well known that the pituitary, posterior lobe, regulates water and the sodium chloride excretion. In contrast to the eclamptic symptoms is the condition diabetes insipidus, in which there is rapid excretion of water. It is thought, therefore, that there is a definite connection between the physiological action of the posterior lobe of the pituitary and the increased production of this hormone during pregnancy. The point of attack of the posterior lobe is frequently in the kidney itself. It was, therefore, deemed advisable to see in this intoxication whether the posterior pituitary could produce the nephritic condition. This was carried out on rats in so-called medium doses (dose not given). Albumen and granular casts were found in the urine and changes in the tubules were found in the kidney. Also the author was able to produce a picture that showed the anatomical and pathological changes analagous to eclampsia. Fauvet showed pictures of thrombosized blood vessels in the liver, and fibrin was found in all the capillaries, also necrosis in the periphery with fatty infiltration. In the kidneys were massed areas of glomeruli and degenerative changes in the walls with hyaline masses in the descending tubules, and albumen and granular casts were found in the urine. In the brain capillaries, hemorrhages were found such as are seen in eclampsia. The experiments indicate that through intoxication with posterior lobe extracts clinical and pathological anatomical changes are

produced, which simulate those seen in the human and the findings permit the statement that there is a toxemia caused by the posterior lobe. Küstner showed that there was a melanophore stimulating substance in the blood of eclamptics and Erhart found it in the placenta of eclamptics. The antidiuretic and blood pressure raising principle produced by the posterior lobe is influenced by narcotics and treatment of eclampsia through narcotics is the foundation of Strogonhoff's method in which chloroform is the antidote for the eclamptic poisoning. It is also shown that narcotics inhibit the action of the posterior secretion.—R. C. Moehlig.

Hyperplasia of the endometrium and the hormones of the anterior hypophysis and the ovaries. Fluhmann, C. F., Surg. Gynec. & Obst. **52:** 1051. 1931.

Hyperplasia endometrii is the name given to a characteristic lesion of the endometrium which should not be considered as a purely local change but as part of a definite clinicopathological entity. It was found in 2.8% of the last 1,700 hospital admissions on the Stanford Gynecological service, and accounted for 12.2% of patients in a series of 507 women with abnormal uterine haemorrhage. It may occur at any time during the active sexual life of women and has been observed in the postclimacteric period, but the majority of cases are found just before and during the menopause. Approximately 75% of the patients were multiparae. The outstanding symptom of the disease is uterine haemorrhage, which is manifested mainly in two ways: (1) Periods of profuse bleeding occurring at cyclic intervals, and (2) prolonged, continuous or intermittent, haemorrhages. No relation between hyperplasia endometrii and systemic disease was established, but in about 30% of the cases there was an associated pelvic disorder. The endometrium is characterized by a marked hyperplasia of both glands and stroma. There is an absence of the corresponding cyclical changes of menstruation and a disorderly arrangement of the glands, of which 3 main types are seen: (1) glands lined by a single layer of cylindrical epithelium; (2) cystic glands with a low cuboidal epithelium; and (3) glands with a stratification of the cylindrical epithelium. In specimens obtained at the time a patient is bleeding may be seen in addition areas of necrosis, thrombosis of blood vessels, and infiltration with leucocytes and lymphocytes. Epidermidalization is occasionally noted and may give rise to confusion with carcinomatous change. A co-existence with carcinoma has been described. The ovaries of patients with hyperplasia endometrii characteristically show the presence of cystic ripening follicles, atretic follicles, and theca lutein cysts, and there is an absence of mature corpora lutea. A number of cases with ovarian new-growths have previously been described, and one additional instance of granulosa cell carcinoma is herein reported. Functional studies have demonstrated an excessive production of oestrin during the course of this disease, and the name "hyperoestrinism" is suggested to describe this condition. In only one case out of 10 was it possible to find large amounts of the anterior pituitary sex hormone in the blood. Evidence is advanced suggesting that hyperplasia endometrii is the direct result of an overstimulation of the endometrium by oestrin and the complete absence of progestin influence. The chief local factor producing haemorrhage is the occurrence of areas of tissue disintegration. Two possibilities regarding the induction of necrosis in the endometrium have been discussed, namely: (1) a sudden cessation of oestrin production, such as would occur consequent to the death of the ovum and atrophy of the follicle; and (2) a prolonged excessive oestrin stimulation such as would result from the persistence of cystic ripe follicles. The etiology of this disease is as yet obscure but it is evidently the result of an endocrine disorder rather than a local pelvic condition. The possible involvement of the anterior hypophysis is considered. The use of repeated curettages in younger patients and intra-uterine radium applications for women of the menopausal age are recommended as the most satisfactory methods of treatment evolved to date.—Author's Summary.

Action of the hypophysis on the sex glands of fish and reptiles (Action sexuelle de l'hypophyse sur les poissons et les reptiles). Houssay, B. A., Compt. rend. Soc. de biol. **106:** 377. 1931.

Injections of hypophysis in one type of fish and transplantation in one type of snake resulted in a very early expulsion of eggs.—J. C. D.

The hypophysis and Bidder's organ (Hypophyse et corps de Bidder). Houssay, B. A. and J. M. Lascano-Gonzalez, Compt. rend. Soc. de biol. **108:** 131. 1931.

Bidder's organ is a rudimentary ovary found in male toads. Over a hundred toads were operated on. Bidder's organ enlarges after castration if the hypophysis is intact. Hypophyseal transplants accelerate the enlargement in castrated animals and produce an enlargement of Bidder's organ in uncastrated. Hypophysectomy causes atrophy of this organ in castrated and uncastrated animals. The anterior lobe is the active portion of the hypophysis.

—J. C. D.

Hyperglycemia in hypopituitarism, with glandular treatment. Kenyon, Josephine H., Abst., in Society Transactions, Arch. Neurol. & Psychiat. **26:** 656. 1931.

A boy, aged 22, was presented as an interesting example of glandular adjustment. He had been observed since he was 15, first as a patient of the Neurological Institute Clinic and later at the Vanderbilt Clinic. At 15 years of age, in 1924, he presented a typical picture of hypopituitarism; he was a short, fat boy with girdle weight, pads of fat over the region of the breast, a large abdomen and small implanted genitals. He was not doing well in school and complained of frequent frontal headaches. The height was 63 inches (160 cm.) and his weight 153 pounds (69.4 kgm.). (The average weight for his height is 111 pounds [50.3 kgm.].) The blood sugar measured 0.187. Urinalysis, blood count and other laboratory tests gave negative results. The roentgenogram showed a sella with heavy dorsum that gave the appearance of closing in of the sella although, due to the separation of the anterior clinoids, this was more apparent than real. The patient was treated for two years with both whole and anterior lobe pituitary extract administered orally and hypodermically. The diet advised was one with a relatively low content of carbohydrate. There was a rapid drop in blood sugar from 0.187 to 0.136 in one month and, when taken at the end of four months, to 0.10. It had varied only slightly from that figure through the succeeding seven years. The urine had never shown sugar. The weight dropped to 128 pounds (57.1 kgm.). After the two years of medication with pituitary was completed, he gradually gained in weight, though on the same diet, but as his height increased in proportion, he never appeared fat again. He lost the pads of fat within the first year of treatment, and when 17 had practically no signs of hypopituitarism. A roentgenogram of the skull taken recently showed a sella of approximately the usual size for the skull. He was faithful in reporting at intervals of six months. He graduated from Junior High School, spent six months in a trade school and has been working as a printer ever since.

Effect of large doses of anterior hypophysis lobe extract on the reproductive ability of the rat (Action des doses élevées d'extrait d'hypophyse antérieure sur l'aptitude du rat a la reproduction). Lepine, P., Compt. rend. Soc. de biol. **107:** 32. 1931.

The follicular atresia and development of corpora lutea which follow such injections in the female, result in temporary sterilization. In males there is reduced reproductive activity without any clear-cut physiological changes.

—J. C. D.

Properties and durability of powdered anterior pituitary lobe (Eigenschaften und Haltbarkeit des Hypophysenvorderlappenpulvers). Loeser, A., Arch. f. exper. Path. u. Pharmakol. **161:** 730. 1931. Abst., Chem. Absts. **26:** 1018.

The sexual hormone in powdered anterior pituitary lobe is destroyed by strong acids, bases and heat. It is insoluble in lipoid solvents, but soluble in acetic, sulfosalicylic and tartaric acids. Its efficiency is not destroyed by ultraviolet rays, but is decreased by H_2O_2 or by the presence of iron. Drying the gland does not affect its hormone properties; and the dried powder has not deteriorated since its preparation.

Ovulation and precocious puberty following parabiosis (Puberté précoce par parabiose et ovulation). Martins, T., Compt. rend. Soc. de biol. **106:** 508. 1931.

In three cases ova have been recovered from the tubes of female rats brought to precocious maturity by parabiotic union with a gonadectomized mate. In two of these cases the mate was a female and in one case a male.

This precocious puberty, due presumably to an excess of anterior lobe substance, is proved to result in actual discharge of ova.—J. C. D.

Regulation of the hypophysis by the testis (La régulation de l'hypophyse par le testicule). Martins, T. and A. Rocha, Compt. rend. Soc. de biol. **106:** 510. 1931.

Immature male rats were parabiotically united to castrated males or females. The castrated member of the pair then received daily injections of testicular material. If the castrated animal was a male this treatment delayed the usual precocious sex development. If the castrated animal was a female there was no modification of the precocious sex development which takes place in the uncastrated member of such a pair. This indicates that the testis has a specific effect on the male hypophysis.—J. C. D.

Some effects of fresh pituitary homo-impiants and of the gonad-stimulating substance from human pregnancy urine on the reproductive tract of the male rat. Moore, C. R. and Dorothy Price, Am. J. Physiol. **99:** 197. 1931.

Fresh hypophysial implants or injections of urinary hebin—the gonad-stimulating substance from human pregnancy urine (Wallen-Lawrence and Van Dyke)—have been followed in prepubertal male rats by: (a) slight increases in gross measurements of the testis; little or no increase in tubular diameter; little, if any, acceleration of spermatogenesis; and decided increase in the interstitial tissue; (b) decided increases in size of the prostate gland and seminal vesicles; (c) marked precocious attainment of secretory differentiation in the seminal vesicles. Urinary hebin injections into normal adult males produced a marked size increase in prostate glands and seminal vesicles; secretion granules were both more numerous and larger. Visible effects on the testis were limited to slight increases in interstitial tissue. Injections of urinary hebin into castrated males were without effect upon the reproductive tract.—Authors' Summary.

The mechanism of the action of pituitrine. Effect of extracts and of substances of the posterior lobe of the hypophysis on the lactic acid of the blood (Sur le mécanisme d'action de la pituitrine. Action de l'extrait et des substances rétropituitaires sur l'acide lactique du sang). Nitzescu, I. I. and N. Munteanu, Compt. rend. Soc. de biol. **106:** 499. 1931.

In dogs and rabbits subcutaneous or intravenous injection of pituitrine results in an increase of lactic acid in both arteries and veins. Vasopressin gives similar results while ocytocin produces a less marked increase.—J. C. D.

Pituitary and ovulation in the hen (Wirkung von Hypophysen-Vorderlappen auf die Ovulation des Huhns). Noether, P., Arch. f. exper. Path. u. Pharmakol. **160:** 369. 1931. Abst., Physiol. Absts. **16:** 559.

The action of anterior pituitary in the hen is specific. By a series of experiments the amount of dried powder necessary to interrupt egg-laying for at least 7 days was determined. The dose-action curve is given. Eighty mgm. of the dried powder were found to be required to stop laying in 5 out of 10 hens for this minimum period, and this amount is selected as the hen unit. This unit is equivalent to 4 rat units.

A contribution to the pathogenesis and heredity of the Laurence-Biedl syndrome (Dystrophia adiposogenitalis, retinitis pigmentosa, mental deficiency and polydactylism). Report of three cases in one family. Ornsteen, A. M., Am. J. M. Sc. **183:** 256. 1932.

Adiposogenital dystrophy, retinitis pigmentosa and mental deficiency are the most constant phenomena of the Laurence-Biedl syndrome in the order given; polydactylism is next and other anomalies of development last. This form of Froehlich's dystrophy is considered herein to be a genotypic inherited unit character defect, because the associated symptoms of the Laurence-Biedl syndrome are found occurring as isolated manifestations of the same order. The frequent association of the first three elements of the syndrome is explained on the basis of a developmental defect of the ectopic zone of the prosencephalon, for the embryological reason that the hypothalamus (infundibulum) and the optic chiasm take origin from the ventral segment and the end brain from the cephalic segment of the ectopic zone of Schulte. The other

developmental anomalies, namely, polydactylism, skull deformities, atresia ani, and others, appear because of the coupling of somatic genotypic defect characters with the cerebral units characters mentioned above.
—Author's Summary.

Anterior pituitary and placenta (Hypophysenvorderlappen und Placenta). Philipp, E., Zentralbl. f. Gynäk. **54**: 450. 1930. Abst., Am. J. Obst. & Gynec. **22**: 656. 1931.

The author believes that the pregnancy reaction of Aschheim-Zondek is in reality a placental reaction. To support this view he submits the following evidence: The chorionic villi of a human tubal pregnancy of two or three months were implanted into infantile mice and without a single exception all showed an enormous change in the ovaries similar to the changes obtained in the Aschheim-Zondek reaction. Amniotic fluid, the amnion itself from an early pregnancy, and decidua curetted from a case of tubal pregnancy, gave a similar, but not so strong, reaction. Similar injections and implantations into castrated mice gave no reaction of estrus. Placental implantations of early abortions gave positive tests in cases which had showed a positive Aschheim-Zondek reaction, and negative tests in cases which had showed a negative Aschheim-Zondek reaction. Implantation of placentae from patients at term gave a very weak reaction discernible only on microscopic serial sections. Direct implantation into mice of anterior pituitary lobes taken directly from four patients, three of whom died postpartum after term pregnancies, and one who died after abortion in the third month, gave no ovarian change. However, implantation of three anterior pituitary lobes taken from non-pregnant women did give typical changes, i. e., follicular bleeding and corpora lutea atretica. The author hesitates to draw too many conclusions from a research which is just beginning, but he does state quite positively that the Aschheim-Zondek reaction results from products of pregnancy and not from the anterior lobe of the pituitary gland.

Fibroma of the uterus and hypophysis. Scaglione, Arch. ital. di ginec. **11**: 2. 1930. Abst., Am. J. Obst. & Gynec. **22**: 656.

It is noteworthy that fibromas develop: (1) Only exceptionally before puberty and after the menopause. It is therefore a tumor that coincides with the greatest activity of the ovary. (2) After menopause many fibromas undergo retrograde changes. (3) Histologic analogies exist between uterine hyperplasia in pregnancy and localized hyperplasia of the foci of myomas. (4) The fibroma is rare in the neck of the uterus, a region not participating in ovarian growth activity. (5) The fibroma is frequent in sterile females. Existing relations between ovary and hypophysis can be thus demonstrated: (1) The total ablation of the anterior lobe of the hypophysis in immature animals leads to a cessation of development of ovary and uterus. (2) Total ablation of the anterior lobe of the hypophysis in mature animals leads to a rapid diminution of the weight of the ovary with stoppage of the maturation of graafian follicles and of ovulation, with disappearance of the corpora lutea. At the same time the uterus undergoes atrophic changes with cessation of its cyclic activity. (3) The homo- and the hetero-transplant of hypophyseal tissue in animals deprived of hypophysis leads to an increase in weight of the ovary, a return of functional activity and an increase in the volume of the uterus. (4) Transplants of hypophyseal fragments to immature animals lead to a rapid increase in weight of the ovary, an increase in the graafian follicles and to a considerable hypertrophy of the uterus. These and other factors would justify the conclusion that the hypophysis exercises a direct effect on a fibroma, possibly since it modifies ovarian activity.

Note on the stimulating action of extracts of the anterior lobe of the hypophysis on the thyroid (A propos de l'action stimulante des extraits préhypophysaires sur la thyroïde).

Specific action of extracts of the anterior lobe of beef hypophysis on the weight of the thymus in young ducks (Action spécifique des extraits préhypophysaires de bouef sur le poids du thymus de jeune canard). Schockaert, J., Compt. rend. Soc. de biol. **105**: 223; 226. 1930.

In 18 young ducks injections of anterior lobe extracts prepared by the method of Evans and Simpson were followed by the histological picture of

overactivity. Lactalbumin, antitetanic serum or terebinthine produced similar results. When both the thymus and the thyroid were examined, however, it was found that hypophyseal extract was the only one which markedly reduced the size of the thymus while exciting the thyroid.—J. C. D.

Body temperature and temperature changes in hypophysectomized dogs and dogs with injured tuber cinerea (Température et réactions thermiques chez les chiens hypophysoprives ou a tuber lésé). Solari, L. A., Compt. rend. Soc. de biol. **108:** 125. 1931.

In 34 dogs the hypophysis was removed and in seven others the tuber injured. Of the former, 10% showed a permanent reduction in body temperature. The others remained normal up to periods of five months. Beta-tetrahydronaphtylamine or dead colon bacilli injected normally cause fever. The response of both groups of operated animals to these agents was normal.
—J. C. D.

Effect of anterior pituitary on leucocyte counts (Verhalten der Leukocyten nach Injektion von Prähormon). Stockinger, W. and F. Berchtold, Ztschr. f. d. ges. exper. Med. **75:** 827. 1931. Abst., Physiol. Absts. **16:** 560.

The preparation used was Prähormon obtained from the urine of pregnant subjects. The effect of injection of 100 units in men was studied. Subcutaneous injection was followed by painful local swelling during 2 hours. Intramuscular injection did not produce these effects. After injection there occurred after 1 to 1½ hours a quickly passing leucocytosis equally involving neutrophils and lymphocytes; this effect was regarded as unspecific. But on the day of injection and for several succeeding days there occurs a great exaggeration of the post-prandial leucocytosis, which may reach values 3 times as great as those before meals. On the first day this leucocytosis involves only neutrophils, but during following days the lymphocytes also become involved. The effect is greatest after protein meals.

Hypopituitary disease with hemiplegia, hypertension, and an atypical sugar tolerance curve. Strecker, E. A., M. Clin. North America, **14:** 835. 1931.

A colored woman of 28 had right hemiplegia, aphasia, and hypopituitary disease of the Fröhlich type. The systolic blood pressure was above 200 and the hemiplegia was obviously due to a cerebral-vascular accident. There was also hyperglycemia with decreased carbohydrate tolerance.—I. B.

Basophilic adenoma of the hypophysis with associated pluriglandular syndrome. Teel, H. M., Arch. Neurol. & Psychiat. **26:** 593. 1931.

The case of a woman of 20 years is reported in which autopsy revealed a basophilic adenoma of the anterior lobe of the hypophysis associated with generalized endocrine hypoplasia including thyroid, adrenal and ovary. The thymus was uninvoluted and the islet tissue of the pancreas was probably increased over the normal amount. The immediate cause of death was epidemic meningitis. However, past history revealed "menstruation" at the age of 9 years, asthenia, obesity and hirsutism; associated with elevated basal metabolic rate and pulse rate. In discussion it was pointed out that the hypophyseal basophilic adenomena might in the light of the recent physiologic and pathologic evidence be looked upon as causative of the syndrome of generalized endocrine hyperplasia and pubertas praecox. The suggestion was offered that perhaps in some cases of pubertas praecox associated with hypernephroma and pineal tumor careful search might reveal hypophyseal basophilic adenoma.
—Author's Abst.

Physiological proof of sympathetic innervation of the pituitary gland (Über den Mechanismus der Ansläsung der Gravidität und Pseudogravidität, zugleich ein physiologischer Beweis für die sympathische Innervation des Hypophysenvorderlappens). Vogt, M., Arch. f. exper. Path. u. Pharmakol. **162:** 197. 1931.

The ablation of the superior cervical ganglia and cervical sympathetic nerves in female rats renders it impossible to provoke pseudopregnancy by mechanical stimulation of the cervix. In such rats, however, coitus with a normal male is followed by a normal pregnancy, and coitus with a vasectomized male is followed by pseudopregnancy. The author interprets these data

as indicating that the mechanical stimulation of the cervix is only accessory to other processes in the production of the reactions of pregnancy and pseudopregnancy. He regards the effect of ablation of the cervical sympathetic as proof of a sympathetic innervation of the anterior lobe of the pituitary.
—Maurice H. Friedman.

Syphilis of the pituitary gland producing acromegaly. Werner, A. A., J. South. Med. Ass. **24**: 953. 1931.

The author reported a case of acromegaly resulting from a syphilitic tumor of the pituitary gland. The patient was a man aged 50 years when he came under observation. Until the age of 42 he had felt perfectly well. At that time he developed an intermittent sensation of pressure over the upper tempora-parietal and occipital regions just above the external occipital protuberance. The pressure sensation seemed deep in the brain, was annoying, but never painful. During the last three years this head pressure was more or less constant. He insists that it was not a headache and claims never to have had headaches. Three years ago he had most of his teeth extracted, thinking that this was the cause of the trouble, without relief. He has never had nausea, vomiting nor visual disturbance. The nasal passages have been almost occluded for 10 years. Four years ago he had turbinectomy and septal operation without relief. He has been unable to breathe through the nose during the last 3 years, except upon effort. Three years ago he noticed that the hands and feet were getting larger. A signet ring which he had worn on the left ring-finger for 12 years became too tight and he transferred it to the left little finger, and now it is too small for that digit. For years previous to one year ago he wore No. 9, double "A" shoes, but now wears No. 12 shoes. Formerly he wore a 7⅜ hat and now he wears a 7⅝. Fatigability and decrease in libido and potency, with slowing of cerebration, decreased memory and ability to concentrate the mind has been noted for the last 3 years. Finger joints would lock upon flexion and would have to be forcibly extended, producing a snapping noise. All tissues of the body increased in size, the features became coarse and heavy, the lips thick, the nose broad and blunt, prognathism developed, the malar eminences, and supraorbital ridges prominent. Marked kyphosis, with peaking of the sternum at the upper one-third, occurred and the typical spade hand developed. Roentgenogram of the hands showed thickening of the bones with typical mushrooming of the ends of the terminal phalanges and hooking of the distal phalanx of the thumb. The pituitary fossa measured 9 mm. vertically and 20 mm. exterior-posteriorly. The region of the anterior lobe shows a rounded increased density, and there is erosion of the bases of the posterior clinoid processes and the upper part of the dorsum sellae. At age 20 years he had a sore on the prepuce which was untreated except for some ointment which he obtained at a drug store and applied locally. Kahn test at time of examination was four plus. The eye grounds were practically negative, because the tumor enlarged backward instead of forward. Intensive treatment with mercurosol and potassium iodide for one year gave great relief from the cranial pressure symptoms. The soft tissues of the face, hands and body in general became more pliable and to a great extent lost their thick, wrinkled, leathery appearance.—Author's Abst.

Influence of female sex hormone and of hormones of anterior lobe of hypophysis on hypophysis of rats (Der Einfluss des weiblichen Sexualhormons und der Hypophysenvorderlappenhormone auf die Struktur der Ratten-und Mäusenhypophyse). Zondek, B. and W. Berblinger, Klin. Wchnschr. **10**: 1061. 1931. Abbreviated Abst., J. A. M. A. **97**: 747.

In order to determine whether the administration of hypophyseal or of sex hormones causes morphologic changes in the cell apparatus of the anterior lobe of the hypophysis, the authors made tests on castrated and on infantile rodents. On the basis of their tests they reach the following conclusions: (1) The morphologic changes in the anterior lobe of the hypophysis which are produced by castration are hardly at all influenced by prolonged administration of either the female sex hormone or the hormones of the anterior lobe of the hypophysis. (2) One administration of the follicle maturation hormone that is produced by the hypophysis effects on the anterior lobe of the hypophysis of the infantile animal a slight degree of maturation. (3) Repeated administration of follicle maturation hormone and of the luteinization hormone (both hypophyseal hormones) effect a marked ripening of the anterior lobe of the hypophysis of the infantile animals.

The relations between the sugar and glutathione in the blood of normal and diabetic individuals (Le rapport entre le taux du glutathion sangiun et la glycémie chez l'Homme normal et chez les diabétiques). Arnovljevitch, V., Compt. rend. Soc. de biol. **107:** 1481. 1931.

In health there are about 100 mgm. of sugar and 40 mgm. of the sulphur compound glutathione per 100 cc. of blood. This gives a coefficient of 2.5 for the normal. In diabetes this ratio may be as high as 9.0. Treatment not only reduces the sugar but increases the glutathione. The return of the ratio to normal is a valuable indication of the effectiveness of the treatment.—J. C. D.

Is insulin itself a specific antigen (L'insuline constitute-t-elle en elle- même un antigène spécifique)? Barral, P. and J. Roux, Compt. rend. Soc. de biol. **106:** 292. 1931.

Shock appeared in guinea pigs after the second injection of beef serum, emulsion of beef pancreas, purified and unpurified insulin. Insulin did not produce shock in animals sensitized with insulin. Insulin by itself would appear to be an antigen.—J. C. D.

A study of the islands of Langerhans in vivo with observations on the circulation. Berg, B. N., Am. J. Physiol. **95:** 186. 1930.

The capillary circulation in the islands of Langerhans can be observed in vivo in the pancreas of the white mouse. Variations in the circulation are due to changes in the afferent arterioles. Intravenous injections of epinephrin and pituitrin cause blanching of the islands by vasoconstrictor action on the arterioles.—Author's Summary.

Experimental and clinical investigation on the treatment of diabetes with insulin by mouth. IV. Liver extract as protector of insulin (Experimentelle und klinische Untersuchungen zur Frage der peroralen Diabetesbehandlung. IV. Mitteilung. Leberextrakte als Resorptionsvermittler der Insulins). Bertram, F., F. Horwitz and E. Wahncau, Klin. Wchnschr. **10:** 486. 1931.

Insulin and insulin plus liver extract are effective when given by mouth only if the stomach be empty of food. The authors believe that liver extract has a protective action on insulin against destruction in the stomach.—M. O. L.

Studies in the intermediary fat metabolism in diffuse parenchymatous lesions of the liver, under the influence of insulin and carbohydrates (Untersuchungen über den intermediären Fettstoffwechsel bei diffusen Leberparenchymläsionen unter Insulin-Kohlehydrateinwirkung). Blöch, J., Klin. Wchnschr. **10:** 937. 1931. Abst., Chem. Absts. **26:** 500.

Insulin causes a fixation of glycogen in the liver; it also counteracts hyperlipemia by causing a fat glycogen change in the liver, and by preventing the liberation of fat from other depots into the blood. Peroral carbohydrates help dispose of the ketone bodies formed as a result of the excessive fat metabolism.

The effect of subcutaneous injections of trypsin on the blood sugar and on insulin action. Buckley, O. B., Brit. J. Exper. Path. **12:** 13. 1931. Abst., Chem. Absts **25:** 4935.

The subcutaneous injection of a single dose of 0.1 cc. Fairchild's sterile glycerinated trypsin into a rabbit is liable to be followed by a transitory rise in blood sugar. This effect on blood sugar is related to the degree of activity of the enzyme. The rise of blood sugar described masks the effect of insulin given subcutaneously at the same time at a different part of the body. When the trypsin is sufficiently inactivated by heat, insulin lowers the blood sugar in the normal way. The subcutaneous injection of a single dose of sufficiently potent trypsin is followed by a period of days in which insulin fails to lower the blood sugar, either completely or partially. Normal insulin action gradually returns. Though there is no definite proof in these results that proteolytic enzymes, such as trypsin, play a part in the state of lessened response to insulin found in septic and toxemic conditions, it is pointed out that an excess of trypsin in the organism has the same effect on insulin action.

Effect of insulin and glucose on normal and obstructed intestine. Gage, I. M., A. Ochsner and R. A. Cutting, Proc. Soc. Exper. Biol. & Med. **29**: 264. 1931.

It is suggested that glucose alone should not be used postoperatively and certainly not in the presence of intestinal obstruction. Glucose alone, in the majority of experiments on dogs, exerted an inhibiting effect on intestinal activity. Insulin, or the combination of insulin and glucose, produced an increase in intestinal activity. The best results were obtained when insulin preceded the administration of glucose by about one-half hour's time. There was no correlation between the intestinal activity and the blood sugar findings.
—Authors' Summary.

The influence of intense external secretory activity in the pancreas on reduction of blood sugar by insulin (L'influence de l'hyperactivité de la fonction exocrine du pancréas sur l'insulinémie).

On the causes of the reduction in output of insulin secretion seen during excessive external secretion of the pancreas (Sur les causes de la frénation de l'insulinosécrétion observée au cours de l'hyperactivité de la fonction exocrine du pancréas). La Barre, J. and Germaine Boolemen, Compt. rend. Soc. de biol. **108**: 227; 229. 1931.

A dog termed the donor was attached by his pancreatic vein to the jugular of a depancreatized recipient. Normally the insulin in the blood of the donor reduced the hyperglycemia in the blood of the recipient. If the pancreatic duct of the donor was tied and the external secretion stimulated by a dose of secretin, the donor's blood lost its hypoglycemic effect. If the donor's acinar tissue was much reduced as a result occlusion of the duct for 40 days, the exocrine activity was associated with some loss of hypoglycemic power. Four experiments in each series are given. The author concludes that the passage of protrypsin and other exocrine products into the islet circulation inhibit the production of insulin.—J. C. D.

Action of insulin on the increased blood cholesterin in nephritic rabbits (Action de l'insulin sur l'hypercholestérinémie des lapins néphrétiques). Mauriac, P., Compt. rend. Soc. de biol. **108**: 54. 1931.

In rabbits rendered nephritic with uranium nitrate, insulin reduces the increased cholesterin in the blood. A similar effect is seen in patients with nephritis.—J. C. D.

The duality of diabetes mellitus and pulmonary tuberculosis. Ritter, J., Illinois M. J. **60**: 371. 1931.

Diabetes predisposes to incidence of tuberculosis. On the other hand, in a number of cases of the coexistence of the two diseases, it was observed that the diabetes status became improved and was even cured with, however, the increased activity of the tuberculous process. Indeed, it has frequently been observed that in a progressive tuberculous process in a diabetic the glycosuria lessens and disappears entirely at the pre-mortal stage of the disease. While the great majority of diabetic individuals do not become tuberculous, those who do have it in severe form. The superimposition of diabetes during the course of chronic phthisis is infrequent, but final phthisis in a diabetic has been frequently observed.—I. B.

On the hypoglycaemic action of insulin upon doubly suprarenalectomized rabbits. Tada, H., Tohoku J. Exper. Med. **17**: 588. 1931.

Insulin was given subcutaneously to 14 rabbits, surviving double suprarenalectomy from 21 to 162 days, and to controls, in such dosage as to invariably cause convulsive attacks in the operated ones. The control experiments were made simultaneously with those on the operated animals. While the convulsive attacks became manifest in nearly all the operated animals, they failed to occur in some of the controls. Hypoglycaemia developed usually much more rapidly in the operated than in the control animals, but there was no material difference in the minimum blood sugar level in both series of animals, decapsulated and non-operated.—Author's Summary.

Effect of insulin treated with acetyl on the volume of the spleen and on arterial pressure in the dog (Action de l'insuline acétylée sur le volume de la rate et la pression artérielle du chien). Teitel-Bernard, A. and C. Parhon, Compt. rend. Soc. de biol. **106:** 673. 1931.

Insulin gives an action on the spleen and blood pressure which resembles that of choline and might result from choline mixed with the insulin. Treatment with acetyl increases the action of choline. Insulin treated with acetyl does not produce this characteristic response so the effect on the spleen and vascular system is not due to choline contaminating the insulin.—J. C. D.

Action of insulin on the isolated mouse uterus (Action de l'insuline sur l'utérus isolé de la souris). Teitel-Bernard, A., Compt. rend. Soc. de biol. **106:** 676. 1931.

Uteri from 15 to 16 gram mice in pro-oestrus were stimulated to contractions of gradually increasing amplitude by insulin.—J. C. D.

Diabetic therapeutics (Diabetestherapie). Thannhauser, S. J., München. med. Wchnschr. **78:** 665. 1931.

The author discusses the general problem of the treatment of diabetes on broad lines and stresses the fact that the dietary treatment is still as necessary as before the insulin era. He divides the sugar utilization by a diabetic in two parts: (1) The transformation of sugar into glycogen and its storage by the liver which requires insulin. (2) The sugar utilization by the muscles wherein the sugar undergoes a synthesis with phosphoric acid estherification (Lactacidogen), which step does not require insulin. It is this latter step wherein even a severe diabetic can utilize a certain portion of sugar without the intervention of insulin. In the dietary treatment he emphasizes the reduction of carbohydrate as well as total calories and the use of large doses of insulin. In coma he thinks that subcutaneous insulin is sufficiently effective and small doses, 3 to 4 mgm., of sodium bicarbonate beneficial. Infections upset the tolerance. The patient should be taught how to give insulin to himself. The insulin resistant cases are merely relative. The doctor should guide the patient, but the patient should be properly instructed in how to carry on.—H. J. J.

The presence of a distinct insulin in depancreatized dogs. Tuttle, G. H., New England J. Med. **206:** 8. 1932.

In 1930, Soskin published very complete studies on the metabolism of depancreatized dogs. Using Soskins tables, the author reaches the following conclusions: (1) It has been shown that a considerable amount of glucose oxidizes or is utilized anaerobically by the depancreatized dog. (2) Since insulin is necessary for the oxidation of glucose, it has been shown that extrapancreatic or cellular insulin must exist in the normal dog after total pancreatectomy. (3) The amount of this insulin gradually increases under the stimulation of the high blood sugar as the experiment progresses. (4) The reason why this insulin can increase thus is because the dog was not naturally diabetic at the time of operation, so that his cellular insulin can be normally increased by carbohydrate stimulation. If he had been naturally diabetic, no such increase or one much less, in proportion to the severity of the diabetic state, would have resulted (because the mechanism for producing cellular insulin may also be deficient in many diabetic states). (5) Muscular action uses up considerable amounts of blood sugar anaerobically without the need of the assistance of insulin; and consequently in diabetic cases where there is a deficiency of insulin such exercise takes the place of a certain amount of insulin in keeping the blood sugar near normal—J. C. D.

Extensive atrophy of subcutaneous fat following the repeated injections of insulin. Williams, J. R., J. Lab. & Clin. Med. **16:** 1911. 1931. Abst., Ann. Int. Med. **5:** 664.

That it is important for the patient self-administering insulin to vary the site of the injection, and equally important for the physician to make occasional physical inspections of the regions used, is shown by the increasing group of cases in which local atrophy of the subcutaneous fat occurs. The author reports and illustrates such a case. A woman, aged forty-four years, who had

been taking two doses of insulin daily for nearly three years, remarked upon the hollows in her thighs. Examination revealed a marked atrophy of the subcutaneous fat on the anterior surfaces of both thighs. The atrophic areas were irregular in shape and from 8 to 15 cms. in diameter with the longer axis parallel to that of the thigh. These cavities were from 2 to 3 cms. deep and gave the impression that the fat had been completely excavated from beneath the skin of the involved areas, for the muscles and blood vessels beneath could be distinctly felt. There was no evidence of soreness or inflammation. Similar changes were noticed in a girl who was taking four small doses of insulin daily. In this case, after avoiding injection of the areas of atrophy for some time, the defects disappeared, apparently being filled in by new fat. The cause of this unusual atrophy is unknown, but a low grade inflammation with fibrosis may be the important factor.

Rate of decalcification and the sites of bone lesions in experimental hyperparathyroidism. Jaffe, H. L., A. Bodansky and J. E. Blair, Proc. Soc. Exper. Biol. & Med. **28**: 793. 1931.

It is suggested that bone resorption and bone deposition are processes that go on in all bone constantly. When the rate of these processes is increased, it is increased in all bone. Both processes are more rapid in the regions of active growth, irrespective of anatomical structure. A mechanism is therefore indicated for rapid decalcification in those regions when a condition is present favoring an excess of resorption over deposition. In regions of less active bone growth, resorption and decalcification proceed more slowly under normal conditions, and a great stimulus is required to produce a considerable degree of resorption. The author examined the skeleton of a large number of young and old guinea pigs, young dogs and rats, suffering from acute and chronic experimental hyperparathyroidism. The resorption lesions were severest and easily produced in the young animals. The metaphyses and the cortex of the shaft of the long tubular bones, the costochondral junctions and the cortex of the ribs used most in the respiratory act, and the bones of the skull and of the lower jaw were the bones and parts of bone most affected. In adults the lesions were produced with greater difficulty and after doses of parathyroid so great that even the epiphyseal ends of the long tubular bones were affected. It is suggested that the same principle applies in experimental rickets and scurvy, which show the localization of the so-called characteristic lesions in the regions of active growth; and in a number of clinical conditions (the so-called osteochondritides), which show localization of lesions in bones (and in regions of bones) of slow metabolic exchange and therefore of slow reparative capacity.
—M. O. L.

Chronic adult idiopathic tetany. Report of a case. Leopold, S. S. and L. Jonas, Am. J. M. Sc. **183**: 418. 1932.

Evidence is presented to indicate that the infantile type of tetany resulting from vitamin D deficiency may be observed in adults, from the same cause. Most of the cases of so-called chronic idiopathic tetany in adults reported in the literature belong to this infantile type, and should be so considered. Chronic adult idiopathic tetany, especially in males, is an excessively rare disease. A patient is reported in whom this diagnosis is justified by the exclusion of all recognized causes for this condition. The opportunity has been had over a period of 4 consecutive years to observe, clinically and by laboratory studies, the effects of various forms of therapy. Calcium lactate by mouth for some unknown reason produced symptomatic relief but failed completely to raise the serum calcium above the tetany level. Viosterol was totally ineffective. Thyroid feeding was followed by an elevation of the subnormal metabolic rate but had no effect either on the tetany or on the serum calcium. Parathormone, subcutaneously administered, produced complete relief of tetany and elevation of the serum calcium above the tetany level during the period of its use. Parathyroid transplant failed completely because the graft probably did not remain alive. The specific effect of parathormone and the total failure of all other therapeutic agents to alter the fundamental state suggest that, in this case at least, chronic tetany resulted from hypoparathyroidism. There are no reports available of histologic studies, ante-mortem or postmortem, of the parathyroid glands in chronic adult idiopathic tetany, hence the pathologic anatomy of this disease is entirely unknown.—Authors' Summary.

Treatment of scleroderma by parathyroidectomy (Essai de traitment de la sclérodermie par la parathyroïdectomie). Leriche, R. and A. Jung, Bull. et mém. Soc. nat. de chir. **57:** 609. 1931. Abst., J. A. M. A. **97:** 355.

Leriche and Jung performed parathyroidectomy on two patients with scleroderma and after some preliminary considerations drew the following conclusions: It is indubitable that scleroderma is a surgical disease. It may be treated by various sympathetic operations or by a parathyroidectomy. At present the results obtained in employing the two methods are equal. The future will tell whether one should combine the two methods or prefer one to the other. Sympathectomy has already demonstrated its well established place and revealed the mechanism of the ailment. In serious cases of parathyroidectomy it has one advantage over sympathectomy. But it seems to invoke general as well as local changes afterward. By both methods one may now cure those patients who have been considered incurable.

On the action of irradiated ergosterol and its products on tetania parathyreopriva (Sur l'action de l'ergostérol irradié et de ses produits dans la tétanie parathyréoprive). Nitzescu, I. I. and G. Popoviciu, Compt. rend. Soc. de biol. **108:** 291. 1931.

Twenty-one parathyroidectomized dogs were studied. The authors summarize by saying that the action of ergosterol-like products, either irradiated, or irradiated and heated, on parathyroid tetany more closely resembles their action on normal dogs than it does their action on rachitic animals. They believe that parathyroid tetany differs from idiopathic tetany since these substances act in the latter as they do in a rachitic organism.—J. C. D.

Effect of parathyroidectomy on the blood calcium (Influence de la parathyroïdectomie sur le calcium sangiun). Weiss, A. G., J. Monguio and L. Bernard, Compt. rend. Soc. de biol. **108:** 12. 1931.

In eight cats removal of one or two parathyroids did not affect the blood calcium.—J. C. D.

Shall the spleen be considered as an organ of internal secretion (La rate doit-elle être considérés comme un organe a sécrétion interne)? Sakharoff, G. P., Rev. franç. d'endocrinol. **8:** 332. 1930.

The spleen is considered an endocrine gland since its removal allows premature development of sex organs in the guinea pig. The germ cells also seem to be affected since the offspring have a stable leucopenia, without any tendency to return to normal. There is also an effect on the transmission of coat color. The author postulates the production of leucocytolysin (a suggestion made previously by Manuokine). These relations he considers as sufficient to place the spleen among the endocrine organs.—B. C.

Origin of Hassall's corpuscles in the pathologic human thymus (La gènese des corps de Hassal dans les thymus humains pathologiques). Bastenie, P., Compt. rend. Soc. de biol. **106:** 55. 1930.

Two hundred glands were studied by the reconstruction method. The corpuscles arise from modifications of mesodermal cells immediately surrounding the capillaries and not from endothelium.—J. C. D.

Physiopathology of status thymo-lymphaticus (Physiopathologie de l'etat thymo-lymphatique). Cattaneo, C., Acta Pediatrica, **11:** 256. 1930.

In the diagnosis of status thymico-lymphaticus there are eight important points: (1) So-called lymphatic habitus; (2) glandular engorgement; (3) Schridde's sign of engorgement of the follicles at the base of the tongue; (4) engorgement of lymph follicles of naso-pharynx; (5) hypertrophied tonsils; (6) enlargement of the nasopharyngeal ring; (7) enlarged spleen; (8) outlining of the thymus by percussion. Other important diagnostic criteria are x-ray examination, increase in lymphocytes, eosinophilia and diminution in platelets Because of the relationship between the thymus and other incretory glands (thyroid, pituitary, adrenals, gonads and perhaps parathyroid) Gattaneo suggests that status thymo-lymphaticus be called status dysendocrino-lymphaticus (etat lymphatique dysendocrinal).—M. B. G.

Relationship of quinine tolerance to thyroid secretion. Bram, I., Northwest Med. **30:** 308. 1931. Abst., J. Nerv. & Ment. Dis. **74:** 769.

Following up his previous studies on the effect of quinine in subjects with exophthalmic goiter and other forms of thyroid disturbance, Bram details his findings in a total of 800 patients studied. Instances of quinine sensitivity and the effect of quinine on the normal individual and on sufferers from thyroid underfunction are also discussed. The conclusions drawn were as follows: (1) The quinine test for thyrotoxemia is a dependable guide in diagnosis, the frequency of error not exceeding 5%. The test does not discriminate between toxic adenoma (true hyperthyroidism) and exophthalmic goiter (Graves' disease). (2) The tolerance for quinine by subjects with hyperthyroidism appears to vary in direct proportion with the height of the basal metabolic rate and is fairly parallel with it, serving as a guide in the progress of the disease. Depending upon the severity of active thyroid oversecretion, the average patient can take from 30 to 90 gr. of quinine sulphate daily for weeks without evidences of cinchonism. (3) Maximal doses of quinine sulphate administered to the average sufferer from hyperthyroidism are of distinct benefit in over 60% of patients and serve as a valuable asset in treatment. (4) From the evidence derived it would a ppear that the physiologic action of maximal doses of quinine sulphate or hydrobromide favors either a curbing of the elaboration of excessive thyroid hormone, or a neutralization of excessive blood-thyroxin, or both.

Some cases of so-called "recurrent thyrotoxicosis." Buchbinder, W. C., M. Clin. North America, **14:** 1267. 1931.

This paper presents two case histories of patients who have recently come to their second operation for the relief of thyrotoxicosis. They represent a group of 19 in a series of 582 consecutive thyroidectomies. The author calls attention to the fact that the disposition of cases of so-called "recurrent thyrotoxicosis" falls largely to the internist, as these patients frequently return to the medical man after surgical measures give no relief. Recurrence of the disease is possible months or years after thyroidectomy restored the normal metabolism and afforded relief of the toxic symptoms.—I. B.

Heart block in toxic goiter. Cameron, J. D. S. and I. G. W. Hill, Edinburgh M. J. **39:** 37. 1932.

This is a report covering two cases. The rarity of these two conditions occurring simultaneously is noted.—J. C. D.

Homoiotransplantation of the amphibian thyroid anlage. Choi, M. H., Folia anat. japon. **10:** (No. 1). 1932.

Thyroid buds from 5-mm. embryos of Bufo japonicus were transplanted to gill pouches of other embryos and a study made of the local development as well as of the rate growth of the embryos. The thyroid bud, if grafted in the region of the gill pounches, can differentiate into follicles which produce colloid substance. No influence on the growth of the host was noted, and the graft is apparently functionless, although it differentiates well in an indifferent area.—Author's Abst.

Treatment of goiter accompanied by hyperthyroidism (Traitement médico-chirurgical des goitres avec hyperthyroids). Demoor, P. and J. Slosse, Rev. franç. d'endocrinol. **9:** 157. 1931.

A review of twenty cases treated either by Lugol's solution or by subtotal thyroidectomy. For the most part there were beneficial results. The data do not lend themselves to abstracting.—B. C.

The level of oxygen exchange in obesity as a factor in planning treatment. Evans, F. A., Ann. Int. Med. **5:** 574. 1931.

Thyroid administration in the treatment of most cases of obesity is not necessary because: (1) A diet consisting of one gram of protein and three-fifths of a gram of carbohydrate per kilogram of ideal weight, and no more than fifteen to twenty grams of fat, gives diets of from four hundred to six hundred calories on which these patients come down rapidly without thyroid. (2) They may be maintained on these diets for months if necessary with

nothing but improvement in their general condition. Thyroid administration in the treatment of most cases of obesity is contraindicated because: (1) The calories per hour oxygen exchange giving a normal basal metabolic rate when calculated on the actual weight, if related to the ideal weight, give a figure considerably higher than normal. This represents one of the physiological strains of obesity which should not be increased by thyroid therapy. (2) The drop in the basal metabolic rates with the institution of limited diets probably accounts for the feeling of well-being and increased resistance to fatigue observed by these patients and in part for the feeling of satiation with the lowered food intake which affords contentment with the diet prescribed. This encourages these patients to persist and should not be eliminated by thyroid medication. A few patients—perhaps no more than 2% of all—do not lose weight rapidly without thyroid medication. These cannot be differentiated from the others by history or physical findings. They may be recognized with assurance only by repeated basal metabolic determinations during the course of dieting.

Experimental studies and the interpretation of the variations in the color reaction of the colloid in thyroid glands (Etude expérimentale et interprétation des variations de la réaction colorante de la colloïde thyroïdienne). Florentin, P., Compt. rend. Soc. de biol. **108:** 70. 1931.

In dehydration the most desiccated follicles stain pink. In entire glands the peripheral follicles containing the older secretion stain pink, while the newly secreted colloid of the centrally placed follicles is blue. The new colloid secreted by guinea pigs under the influence of eserine salicylate takes a blue stain, the older colloid is pink. A concentrated gelatine solution stains pink, a more watery solution blue. These facts indicate that the color of the colloid in stained sections of thyroid is evidence of the degree of dehydration at the time it was fixed and not evidence of changes in chemical composition.

—J. C. D.

Cholesteremia in certain diseases of endocrine glands. Hillmann, M. L. Vrach. dielo. **14:** 13. 1931. Abst., J. A. M. A. **97:** 894.

Hillmann reports his studies on cholesteremia in certain disorders of the endocrine glands, chiefly of the thyroid. Twenty persons were examined: twelve with exophthalmic goiter (all women with the exception of one) and the rest with various other endocrine disorders. In exophthalmic goiter the figures for the cholesterol content were below normal in five cases and slightly above normal in six cases. In all cases of hypothyroidism the cholesterol content of the blood was above normal. Cholesteremia is higher in old persons than in young or middle-aged ones. The author concludes by stating that cases characterized by lowered function of the thyroid present a higher cholesterol content of the blood. In regard to exophthalmic goiter there was no regularity observed. The data obtained by the author in his studies on cholesteremia cannot be used either for diagnostic or for prognostic purposes. The material investigated was too limited to enable one to draw any definite conclusions in this direction.

Blood picture in six hundred cases of goiter. Jackson, A. S., J. A. M. A. **97:** 1954. 1931. Abst., A. M. A.

From a study of 600 cases of goiter, the author draws the following conclusions: The blood picture in hyperthyroidism does not vary essentially from that in the normal person. The differential blood count in hyperthyroidism is not of diagnostic and prognostic significance. There is not a definite relationship between the blood picture and the basal metabolic rate. The lymphocyte count is not varied by an increase or a decrease in metabolism. The blood count is not influenced by the severity of the disease, considering metabolism and weight loss as paramount factors. A secondary anemia is not typical of hyperthyroidism. A leukopenia is not characteristic of hyperthyroidism. Sex and age do not influence the blood picture in toxic goiter. In spite of clinical improvement, no appreciable change was observed in the blood count following the use of iodine in hyperthyroidism. The only appreciable change in the differential blood count in goiter was observed following thyroidectomy for exophthalmic goiter. An increase in the polymorphonuclear count and a decrease in the lymphocyte count occurred. The author does not believe that the blood picture in hyperthyroidism is of any practical clinical importance.

Prevention of goiter in Detroit and Cleveland. Kimball, O. P., J. A. M. A. **97:** 1877. 1931. Abst., A. M. A.

The author presents a comparative study of the prevention of goiter in Detroit and in Cleveland which demonstrates how quickly any community can completely eradicate endemic goiter when there is a unity of all the forces that direct its public health. Without this unity, public health cannot take care of itself. The safety of present methods of prevention of goiter also are considered. Detroit and Cleveland are practically the same size, and as far as is known the natural conditions and the factors determining endemic goiter are the same. The author has been intimately connected with the work in the two cities. In Detroit this preventive measure had the leadership and cooperation of the state department of health, the city department of health, the school board, school physicians and the medical profession. In Cleveland there has been no unity of thought or action. By the prevention of endemic goiter, Michigan has eliminated from her schools in the future thousands of cases of feeblemindedness (cretinoid type), which have in the past and would in the future result from endemic goiter. The rapid disappearance of endemic goiter among school children throughout Michigan is one of the outstanding achievements in preventive medicine.

The dependence of thyroxine effect upon nutrition (Über die Abhängigkeit der Thyroxinwirkung von der Ernährung). Kommerell, B., Arch. f. exper. Path. u. Pharmakol. **161:** 173. 1931. Abst., Chem. Absts. **26:** 1010.

The susceptibility of thyroidectomized dogs to subcutaneous injection of thyroxine is greater if they are on a meat diet. The increased basal metabolism begins later and lasts 2 days longer than it does if they are on a carbohydrate diet, and the respiratory quotient falls lower.

New experiments on the antagonism between the thymus and the thyroid (Nouvelles recherches sur l'antagonisme du thymus et du corps thyroïde). Krizenecky, J., Compt. rend. Soc. de biol. **106:** 325. 1931.

Turtle doves were fed thyroid and thymus as well as thyroid and nucleic acid. The former group lost less weight than the latter and than thyroid-fed controls. Thyroid and thyroid-thymus-fed birds ate about the same amount of food. Starving birds lost weight less rapidly with the combination dose than with thyroid alone. The thymus has therefore a specific antagonistic action for the thyroid which is not dependent on the nucleic acid in it.—J. C. D.

Pathogenesis of goiter. Markowitz, B., Am. J. Clin. Path. **1:** 321. 1931.

The maintenance of a balance between colloid storage (supply) and lack of colloid (demand) seems to be the function of the thyroid gland. With increased demand, due to an unknown stimulus, hyperplasia results and when the demand is met the gland involutes with production of colloid. The simple colloid goiter is only an end result of hyperplasia which is mild and not rapid in its course. Nodular colloid goiter is of similar origin, but differs in that the hyperplasia-involution cycle occurred only in certain areas. Toxic nodular colloid goiter or toxic adenoma is also of the same origin, but here while the hyperplasia-involution cycle occurs there are a few areas of hypo-involution in which hyperplasia persists. True hyperplastic or exophthalmic goiter is one in which there is marked very rapid and unarrested hyperplasia not followed by any form of involution.—Author's Abst.

Focal cyclic growth as a factor in production of nodular goiter. Markowitz, B., Am. J. Clin. Path. **2:** 57. 1932.

There are two distinct processes in the physiology of the thyroid gland which produce a constant hyperplasia-involution cycle: (a) Process of thyroid secretion—active with hyperplasia. (b) Process of accumulation of colloid—passive with involution. These two processes occur as functional cycles and when in disproportion produce nodulation either by one of these two secretions overwhelming the other or by exaggeration of both processes.

—Author's Abst.

Thyrotoxic circulatory symptoms with low metabolic rate. Morris, R. S., Am. Heart. J. **6**: 730. 1931. Abst., Canad. M. A. J. **25**: 741.

The author in this article presents four cases to show that the basal metabolic rate, while very helpful when elevated, is a sign which should be ignored when normal or subnormal in presence of unmistakable evidence of thyrotoxic signs and symptoms. It is pointed out that the thyroid heart is the one type of preventable heart disease and that in all patients with cardiac neurosis the possibility of disease of the thyroid should never be lost sight of. All cases presented showed definite signs of thyrotoxic circulatory disturbance. The basal metabolic rates ranged from —32% to +7%. In all cases subtotal thyroidectomy brought about clinical recovery.

Effect of bleeding and of a single injection of Collip's parathormone on blood calcium, sugar and cholesterin in normal, hyperthyroid and thyroidectomized animals (Action de la saignée et d'une injection unique de parathormone de Collip sur la calcémie, la glycémie et la cholestérinémie des animaux normaux, éthyroidés ou hyperthyroidisés). Parhon, C. I., H. Derevici and M. Derevici, Compt. rend. Soc. de biol. **104**: 437. 1930.

Twenty dogs were used. The parathormone reduced the sugar in normal and thyroidless dogs and had no effect in hyperthyroid animals. It increased the calcium in all animals and likewise the cholesterin in the controls. In the thyroidectomized and hyperthyroid dogs, however, there was an increase of cholesterin.—J. C. D.

On the total phosphorus of the brain and spinal cord of dogs treated with thyroid gland, thyroxin, parathyroid hormone or with thyroid and parathyroid combined (Sur le phosphore total du cerveau et du cervelet chez les chiens traités par le corps thyroïde ou la thyroxine, par l'hormone parathyroïdienne, ou soumis au traitement combiné thyro-parathyroïdien). Parhon, C. I. and G. Werner, Compt. rend. Soc. de biol. **107**: 402. 1931.

Collip's parathormone was used. The phosphorus was increased by all types of treatment. There was a maximum increase of about 12%. This was with thyroid feeding alone.—J. C. D.

Research studies and clinical results on diathermy of the thyroid on the essential metrorrhagias. Paroli, Arch. di Biol. Norm. e Patol. **84**: 1. 1930. Abst., Am. J. Obst. & Gynec. **22**: 655.

In the metrorrhagias of puberty one often observes a functional deficiency of the thyroid. After the diathermic treatment of the thyroid greater activity of this gland is noticed while at the same time the metrorrhagias improve and eventually cease. Such improvement lasts only three or four months. In all cases of metrorrhagia near the climacterium sterilizing Roentgen or radium therapy is preferable.

On the action of thyroid gland and of thyroxine on moulting and feather structure in geese. Raspopova, N., J. Medico-Biologique, **2**: 52. 1930.

Moulting in geese is not observed when fed with 40-50 gms. of the thyroid gland. Some increase in the amount of the down part of the feather is being noted. When fed with larger doses of thyroid gland (100 gms.) and after injection of 50 mgm. of thyroxine an energetic moulting is observed. The regenerating feather shows some increase in the amount of down. When fed thyroid gland in the autumn (50 gms.) a complete moulting is observed as well as a considerable increase in the down of the feather in comparison with the spring moulting. Upon injection of 30 mgm. of thyroxine the feather becomes softer and is more easily pinched off.—Author's Summary.

A clinical study of myxedema in Michigan. Riecker, H. H., J. Michigan M. Soc. **30**: 831. 1931. Abst., Ann. Int. Med. **5**: 1042.

From a study of the geographical distribution of 64 cases of myxedema in the series studied, and in comparison with the usual clinical experience in other regions, it is concluded that this disease is more common in the Great Lakes goiter district than in non-goitrous regions. In the series studied, 75% of the

patients were female; and 34 of the 64 were in the age-group 41-60. In 40% the basal metabolic rate was between 15% and 25% below normal. The most common presenting symptom of the patients in this group was weakness. One organ or system was frequently noted to present outstanding signs or symptoms. Anemia, skin lesions, mental and cardiac complaints, and digestive disturbances illustrated this point. Obesity emphasizes rather than submerges the characteristics of the disease.

On the action of thyroxine on the bile secretion. Sacharoff, V., J. Medico-Biologique, **2**: 46. 1930.

Hyperthyroidation of dogs by thyroxine and thyroid gland causes in many cases a successive decrease of the amount of bile secreted into the bile bladder. The action of thyroxine and of the thyroid gland when appreciated by the above method is alike and the thyroid hormone, i.e., thyroxine, is to be regarded as the active substance in both the cases. The successive character of bile secretion decrease agrees with the general conception of the thyroid hormone as of one whose action is successive and durable. The great resistance of "bile-dogs" against hyperthyreosis supports the suggestion and confirms the data according to which thyroxine and its derivatives are being excreted by liver together with the bile. In all the experiments on the bile-secreting function of liver in animals hyperthyreoidized by the thyroid gland it is necessary to take in to account the influence of meat and of the meat component of the gland on the bile secretion.—Author's Summary.

Familial overthyroidizing in chickens (Hyperthyroïdisation familiale chez les gallinacés). Sainton, P. and H. Simonnet, Compt. rend. Soc. de biol. (Paris), **106**: 344. 1931.

Thyroid was fed to two hens and a cock. The usual loss of pigmentation in the feathers occurred. Reproduction was not impaired but the young chicks also showed a loss of pigment instead of usual color in their plumage.

—J. C. D.

Fat tolerance in experimental hyperthyroidism. Simonds, J. P. and Opal E. Helpler, J. A. M. A. **98**: 283. 1932. Abst., A. M. A.

The authors carried out experiments to determine the effect of hyperthyroidism on the fat and lipoid content of the blood after the administration of 2 cc. of olive oil for each pound of body weight. Fifteen dogs were used. The animals showed rather marked individual differences in the fat content of their blood at the beginning of the experiment and in the degree of lipemia produced by feeding the amount of olive oil used. The cholesterol content of the blood bore no definite relation to the neutral fat present. In general, the initial blood fat, i.e., in the sample taken just prior to feeding the oil, was lower during the period of hyperthyroidism than before thyroid feeding was begun, and the administration of 2 cc. of olive oil for each pound of body weight induced a less marked rise in the total lipid content of the blood. After these animals were allowed to recover from hyperthyroidism, their fat tolerance returned to approximately its normal level. During this period of recovery, however, a very noteworthy increase in blood cholesterol was observed. During the period of hyperthyroidism the thyroid gland underwent marked atrophy, sometimes weighing less than 1 gm. The total lipids of the blood as determined by chemical means did not always correspond with the gross lipemia determined by the degree of opalescence or turbidity of the plasma; i.e., a plasma that showed only a moderate gross lipemia contained as much fat and cholesterol as another sample that was quite turbid.